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 statistical analysis plan: *24 July 2024*

KEZAR LIFE SCIENCES, INC.

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

24JUL2024

Statistical Analysis Plan

Version 1.0

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Protocol Number: KZR-616-202

SAP Version: 1.0

SAP Date: 24 July 2024

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	adverse event
AESI	adverse event of special interest
anti-dsDNA	anti-double stranded deoxyribonucleic acid
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
CDE	Center for Drug Evaluation
CEC	Clinical Endpoint Committee
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CP	conditional power
CRO	contract research organization
CRR	complete renal response
CS	clinically significant
DNA	deoxyribonucleic acid
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMEA	Europe, Middle East, and Africa
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EQ VAS	EuroQol visual analog scale of general health
ETV	Early Termination Visit
EULAR	European Alliance of Associations for Rheumatology
FMV	first morning void
GCP	Good Clinical Practice
GTI	Glucocorticoid Toxicity Index

Abbreviation	Definition
GTI-AIS	GTI – Aggregate Improvement Score
GTI-CWS	GTI – Cumulative Worsening Score
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HIV	human immunodeficiency virus
IA	interim analysis
IC	informed consent
ICH	International Council of Harmonisation
IDMC	Independent Data Monitoring Committee
IE	intercurrent event
ITT	intent-to-treat
IV	intravenous
KZR-616	zetomipzomib
LDL	low-density lipoprotein
LN	lupus nephritis
MCMC	Markov Chain Monte Carlo
MCP	metacarpophalangeal
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMF	mycophenolate mofetil
MMRM	mixed model for repeated measures
MP	methylprednisolone
MPA	mycophenolic acid
MPS	mycophenolate sodium
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NRI	non-responder imputation
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PP	per-protocol
PRO	Patient Reported Outcome

Abbreviation	Definition
PRR	partial renal response
PT	preferred term
QTcF	QT interval with Fridericia's correction
RBC	red blood cell
REGPMM	monotone regression with the predictive mean matching
RNA	ribonucleic acid
RTSM	Randomization & Trial Supply Management System
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDRD	Study Deviation Rules Document
SF	screen failure
SIR	systemic injection reaction
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SOC	system organ class
SSR	sample size re-estimation
TB	tuberculosis
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
VAS	visual analog scale
WHO	World Health Organization
WOCBP	women of childbearing potential

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses and data presentations for Kezar protocol 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", Version 1.0, 27 January 2023. It contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety as well as exploratory assessments. The exploratory analysis for reporting of gene expression/pharmacogenomic, urine biomarker, and pharmacokinetic data are outside the scope of this document (see Section 8.6.2, Section 8.6.3, and Section 10 for details). Details regarding the content and frequency of study data reporting to the Independent Data Monitoring Committee (IDMC) can be found in the IDMC Charter. Details regarding the adjudication process for the primary endpoint and manual review of other study data by the Clinical Endpoint Committee (CEC) can be found in a separate CEC Charter. This SAP is based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 and E9 guidelines; (ICH-E9, 1998; ICH-E3, 1995).

Zetomipzomib (KZR-616) is a tripeptide ketoepoxide selective inhibitor of the immunoproteasome. 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. Weekly administration of zetomipzomib demonstrates anti-inflammatory effects without altering the overall function of the immune system. Weekly doses of 45, 60, and 75 mg were well tolerated; the most common AEs at any dose were mild and transient injection site reactions. Signs/symptoms of systemic injection reactions (SIRs) include hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills.

Zetomipzomib treatment was also associated with clinically meaningful reductions in proteinuria in patients with difficult-to-treat LN and appeared to ameliorate signs and symptoms of systemic lupus erythematosus (SLE). In addition, to date, there has been no evidence of immunosuppression such as depression of immune-specific cell lines or impaired function that would be associated with opportunistic infections or serious infections.

Study KZR-616-202 is a Phase 2b, randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the efficacy and safety of zetomipzomib in patients with active LN. For additional details regarding the study design, please refer to Protocol KZR-616-202.

2. 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.

Specific efficacy, safety, and exploratory objectives are as follows:

Primary and Secondary Efficacy Objectives

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.

Primary Safety Objective

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.

Exploratory Objectives

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

- 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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

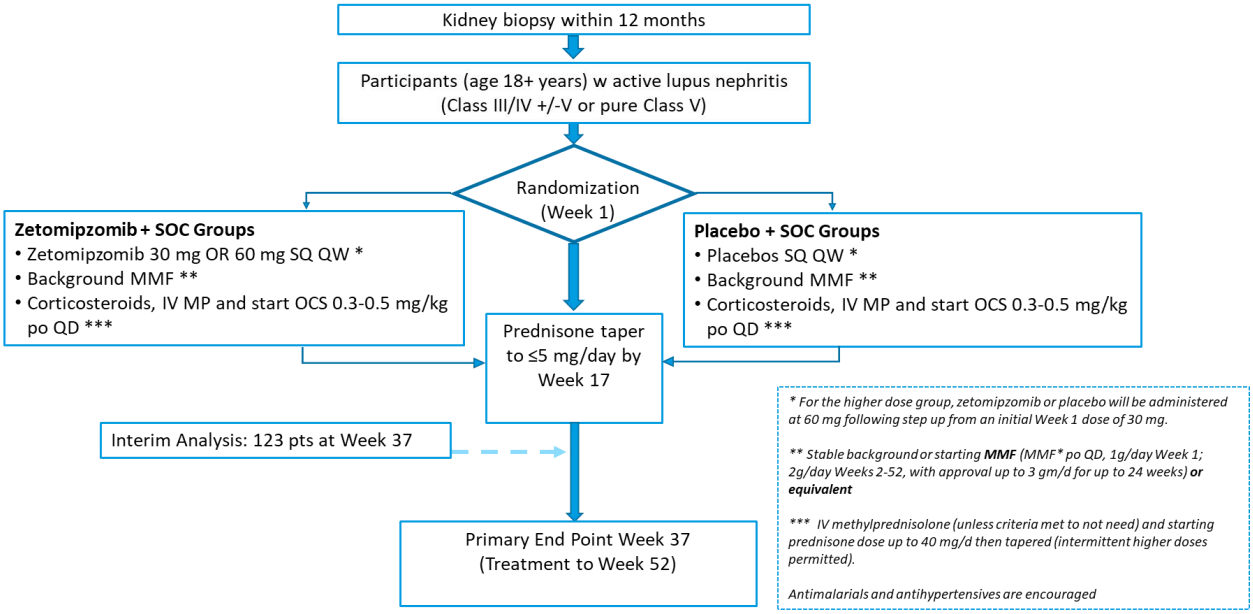
This is a Phase 2b, randomized, double-blind, placebo-controlled, global, multicenter study to evaluate efficacy and safety of zetomipzomib in patients with active Class III/IV +/-V LN or pure Class V LN described in Figure 1. The study will enroll approximately 279 patients: 249 patients with biopsy-proven Class III/IV +/-V LN with urine protein creatinine ratio (UPCR) ≥1.0 and up to approximately 30 patients with pure biopsy-proven 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 pooled 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.

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.

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 intravenous (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.

Patients will be evaluated for eligibility according to the inclusion/exclusion criteria (see Sections 4.2 and 4.3 of the study protocol) 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, ECGs, and clinical laboratory tests and by recording and analyzing all treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Blood samples for sparse and optional pharmacokinetic (PK) collection will also be drawn. Time points for all efficacy, safety, and PK assessments are detailed in the Schedule of Assessments (Appendix 1).

Figure 1: 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. For the higher dose group, zetomipzomib or placebo will be administered at 60 mg following step up from an initial Week 1 dose of 30 mg. 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.

Patients who permanently discontinue study treatment for any reason will be encouraged to remain in the study as outlined in the Schedule of Assessments (Appendix 1) through End of Study (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.

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 (CP).

The study will evaluate efficacy and safety as primary objectives as well as secondary and exploratory objectives to evaluate other potential clinical benefits and pharmacokinetics. Each dose of zetomipzomib (30 mg and 60 mg) will be compared to pooled 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. Study Endpoints

The efficacy, safety, and exploratory objectives and corresponding endpoints are presented in Table 1 below.

Table 1: Study Endpoints

Objectives	Endpoints
Primary Efficacy	
To compare the efficacy of zetomipzomib with that of 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	• Proportion of patients achieving CRR at Week 37
Secondary Efficacy	
To compare the efficacy of zetomipzomib with that of 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	**Key Secondary:** • Proportion of patients achieving PRR at Week 37 • Proportion of patients achieving CRR at Week 53 • Proportion of patients achieving PRR at Week 53 • Proportion of patients achieving CRR at Week 25 • Proportion of patients achieving PRR at Week 25
	Other Secondary: • Percentage change from Baseline in UPCR by visit • Time to CRR • Time to PRR • Time to UPCR ≤ 0.5 • 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 ≤ ULN at Weeks 25, 37, and 53 • Change from Baseline in clinical SLEDAI-2K score, excluding complement and anti-dsDNA components • Change from Baseline in EuroQol 5-Dimension 5-Level (EQ-5D-5L)

Objectives	Endpoints
Safety	
To determine the safety and tolerability of zetomipzomib in patients with active LN on background standard of care, MMF or equivalent, and corticosteroids.	• Incidence and severity of TEAEs • Clinical laboratory tests (hematology, serum chemistry, urinalysis, coagulation, other) • Vital sign measurements (height/weight, body mass index, body temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate) • Physical examination 12-lead ECG assessments
Exploratory Efficacy	
• 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	• 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 LDL cholesterol, serum total cholesterol, serum triglycerides) • Change from Baseline in blood HbA1c • Change from baseline in the GTI as measured by the GTI-CWS and the GTI-AIS • Proportion of patients with Baseline SLEDAI-2K, excluding renal components, ≥6 with at least a 4-point improvement

Objectives	Endpoints
	• Change from Baseline in SLEDAI-2K • Change from Baseline in 28-joint counts • Change from Baseline in 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 • Time to antibodies normalization or negative status (anti-dsDNA antibody normalization, anti-C1q antibody negative status) • Time to complement (C3, C4) no longer being low • Change from Baseline in IgM, IgG, and IgA • Change from Baseline in renal biopsy histopathology and immunohistopathology (optional)* • Pharmacogenomics profile (RNA sequencing) and biomarkers* • Pharmacokinetics profile*

* Endpoint is outside the scope of this SAP.
anti-dsDNA=anti-double stranded DNA; C1q=C1q Autoantibody; CRR=complete renal response; C3=Complement Component 3; C4=Complement Component 4; DNA=deoxyribonucleic acid; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EQ-5D-5L=EuroQol 5-Dimension 5-Level; GTI=Glucocorticoid Toxicity Index; GTI-CWS=GTI Cumulative Worsening Score; GTI-AIS=GTI Aggregate Improvement Score; HbA1c=hemoglobin A1c; LDL=low-density lipoprotein; LN=Lupus Nephritis; MMF=Mycophenolate Mofetil; PGA=physician global assessment; PRR=partial renal response; RNA=ribonucleic acid; SLE=Systemic Lupus Erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; TEAE=Treatment-Emergent Adverse Event; ULN=upper limit of normal; UPCR=urine protein to creatinine ratio.

3.2.1. Definitions Related to Study Endpoints

Baseline values for 24-hour UPCR and all other endpoints are defined in Section 4.
See Section 8 for additional information related to the efficacy endpoints.

3.2.1.1. Complete renal response (CRR)

- A UPCR ≤0.5 in one 24-hour urine sample (for Weeks 13, 25, 37 [primary endpoint], and 53)
- An estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 or no confirmed decrease of >20% from Baseline eGFR.
- For primary endpoint at Week 37, CRR must be adjudicated by CEC

3.2.1.1.1. Calculations Associated with CRR

UPCR is the ratio of urine protein to urine creatinine in the 24-hour urine sample, where urine protein and urine creatinine are expressed in the same units.

eGFR is 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

3.2.1.2. 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.

3.2.1.3. Time-to-event endpoints

When calculating the time-to-CRR or time-to-PRR endpoints, all timepoints where UPCR data is collected will be considered. The UPCR criteria for CRR/PRR may be met using the 24-hour urine tests for Weeks 13, 25, 37, and 53. For all other timepoints, UPCR criteria for CRR/PRR will use 2 consecutive first morning void (FMV) urine tests.

When calculating time-to-FMV-CRR and time-to-FMV-PRR endpoints, if the 24-hour urine test is not available, then 2 consecutive FMV urine tests may be used at Weeks 13, 25, 37, and 53. For all other timepoints, UPCR criteria for CRR/PRR will use FMV urine tests.

Any time the 24-hour urine test is available and valid it should be used for analysis over the FMV urine test (Weeks 13, 25, 37, and 53).

3.2.1.4. Treatment Failure

A patient experiencing one or more of the following criteria define treatment failure:

- Prednisone or equivalent* beyond that permitted (see Section 6.2.1.2 of the study protocol), to include:
  - >10 mg/day for ≥3 consecutive days or for ≥7 days in total during the 8 weeks prior to the renal assessment at
- MMF or equivalent* >2 g/day after Week 25
- Requiring rescue therapy (see Section 6.2.3 of the study protocol for details), as verified by the CEC

- Use of prohibited medications (see Section 6.2.4 and Appendix 2 of the study protocol for details) or inappropriate use of the required concomitant medications (see Section 2.2.5 of the study protocol), as determined through manual data review by the CEC
- 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. See Section 8.1.2 of the study protocol for individual patient stopping rules.

Treatment failure will be adjudicated in blinded fashion by the CEC. Details of this process will be provided in the separate CEC Charter.

**See Appendix 2 for dose conversion of other corticosteroid medications to prednisone equivalent and conversion of mycophenolic acid (MPA) and mycophenolate sodium (MPS) to MMF equivalent.*

3.2.1.5. Relapse

Relapse is defined as loss of CRR at 2 consecutive time points

3.2.1.6. Proteinuric flare

Proteinuric flare is defined as doubling from lowest baseline or post-baseline UPCR and at 2 consecutive time points:

- If patient achieved CRR, then doubled UPCR value must be >1 at 2 consecutive time points to be considered a flare
- If patient achieved PRR, then doubled UPCR value must be >2 at 2 consecutive time points to be considered a flare

3.2.1.7. Time to death or renal-related events

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

- Death
- Doubling of serum creatinine from the baseline value
- Proteinuric flare
- Kidney failure (receiving dialysis or kidney transplantation)

3.2.1.8. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) 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. A SLEDAI-2K of 6 or more generally represents moderately to severely active disease.

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

See Appendix 7 and Appendix 8 for additional information.

3.2.1.9. 28-Joint Count

The following 28 joints will be evaluated separately for tenderness and swelling: 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. For both tenderness and swelling assessments, possible joint count ranges from 0 to 28, with higher counts associated with widespread tenderness or swelling.

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

See Appendix 9 for additional information.

3.2.1.10. Physician Global Assessment (PGA)

The Physician Global Assessment (PGA) is used by the Investigator to quantify disease activity and is measured using an anchored visual analog scale (VAS). The Investigator will assess the patient's current disease activity from a score of 0 (none) to 3 (severe) on a 100-mm continuous VAS, with the assessment made relative not to the patient's most severe state but to the most severe state of SLE per the Investigator's assessment.

See Appendix 10 for additional information.

3.2.1.11. EuroQol 5-Dimension 5-Level (EQ-5D-5L)

The EQ-5D-5L is a patient reported outcome (PRO) that measures health-related quality of life.

The EQ-5D-5L Questionnaire is a 5-question survey where each question corresponds to a health domain (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression), and patients will provide an ordinal 5-level response that reflects their perceived quality of life, with higher values indicating greater disability or worse health. The patient's reported response to each domain will form a 5-digit health status profile, or "health state".

A numerical index value will be assigned to each EQ-5D-5L health state, reflecting how good or bad the health state is according to country-specific preferences. The country-specific collection of index values for all possible EQ-5D-5L states, or "value set", is derived from reference population values using composite time trade-off and discrete choice experiment methods. In the event that a value set is not available for a country in the study, the value set from the closest available country will be used. Parameter estimates derived by Roudijk et al (Roudijk et al., 2022) will be used to calculate patients' utility index scores based on their responses to each question in the survey.

The patient will also rate their own overall health on a 100 mm continuous vertical EQ VAS of general health, where 100 corresponds to the best possible health.

See Appendix 11 for the EQ-5D-5L survey and EQ-VAS of general health.

3.2.1.12. Glucocorticoid Toxicity Index (GTI)

The GTI is a comprehensive, outcome-based glucocorticoid toxicity monitoring instrument that calculates a composite index score from data collected in 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).

The GTI instrument uses two scores: the Cumulative Worsening Score (GTI-CWS) and the Aggregate Improvement Score (GTI-AIS). See Section 8.7 and Appendix 6 for derivation details.

3.3. Study Treatment

Zetomipzomib or placebo ("study treatment") will be administered by subcutaneous injection once weekly from Week 1 to Week 52 according to the Schedule of Assessments (Appendix 1). 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.

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.

See Section 7.1.1.1, Section 7.1.1.2, and Section 7.1.1.3 for information regarding protocol-required background medications (IV methylprednisolone, MMF, and oral corticosteroids, respectively).

3.4. Dose Adjustment/Modification

3.4.1. Dose Modification

Patients in the 30 mg dose group

No dose reduction is permitted.

Patients in the 60 mg dose group

Patients who experience a treatment-related AE will be permitted to undergo dose reduction to the 30-mg dose of zetomipzomib or placebo for subsequent doses. The dose reduction was to be in consultation with, and approval from, the Medical Monitor 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. 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.

All dose modifications should be documented in the electronic case report form (eCRF).

3.4.2. Missed Doses

Doses should be administered within the visit windows as per the Schedule of Assessments (Appendix 1). Any doses administered outside the visit window will be considered a study 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 (see Section 8.1.2 of the study protocol) may resume administration of zetomipzomib or placebo after discussion between the Investigator and Medical Monitor. Upon resumption of dosing, subsequent doses will be timed according to the original dosing schedule based on Day 1 (Week 1). Patients who are discontinued for missed doses will have their discontinuation recorded in the eCRF based on the reason the doses were missed (eg, AE or non-compliance with study treatment). 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 study assessments 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.

3.5. Randomization, Stratification, and Blinding

Patients who have provided informed consent (IC) and passed study inclusion/exclusion criteria per Sections 4.2 and 4.3 of the study protocol will be randomized via the [redacted] system.

Patients will be randomized to receive either zetomipzomib (30 mg or 60 mg) or matching placebo in a 2:1:2:1 ratio (zetomipzomib 30 mg: 30 mg matching placebo: zetomipzomib 60 mg: 60 mg matching 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.

All study personnel and patients may know if the patient is in the low dose group (30 mg or matching placebo) or the high dose group (60 mg or matching placebo). Randomized treatment assignment within dose group (ie, to zetomipzomib or matching placebo) at the patient level will remain blinded to all patients and all Sponsor, contract research organization (CRO; [redacted]), and site personnel involved in the day-to-day conduct of the study until the proper unblinding procedures have been followed. To preserve the blind with respect to active treatment and placebo, patients randomized to the placebo group will receive a subcutaneous injection in an equivalent volume to the active zetomipzomib injection and on the same dosing schedule.

Additional details regarding planned unblinding during the course of the study are documented in a separate Blinding Management Plan. Details regarding emergency unblinding of a patient due to safety concerns are documented in Section 3.2.3 of the study protocol and the [redacted] User Manual. Any patients unblinded for safety reasons will be clearly identified in the data listings.

4. GENERAL STATISTICAL CONSIDERATIONS

This section presents general rules for the derivation and reporting of study data. If a subsequent section related to a specific derivation or analysis differs from this general guidance, the subsequent section takes precedence.

Unless specified otherwise, all study data will be summarized using descriptive statistics. Descriptive statistics for continuous data include number of patients (n), mean, standard deviation (SD), median, quartiles, minimum, and maximum. Categorical data will be described using frequency counts and percentages in each category.

Mean, median, and quartiles will be displayed to one level of precision greater than the data as originally collected. Standard deviation will be displayed to two levels of precision greater than the original data. For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as the original data.

When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for missing values. Unless otherwise specified, the denominator for all percentages will be the number of patients in that treatment group within the analysis set of interest. Percentages will be presented to one decimal place except for the display of 100% frequency which will be displayed as 'XX (100)'.

P-values ≥0.001 will be presented to 4 decimal places as "0.xxxx". P-values <0.001 will be presented as "<0.001". P-values >0.999 will be presented as ">0.999". Confidence intervals (CIs) will be displayed to one level of precision greater than the data as collected.

Treatment groups will be labeled as "Zetomipzomib 60 mg", "Zetomipzomib 30 mg", and "Placebo". In general, all tables and figures will be presented by treatment group. All study data will be presented in by-patient data listings sorted by treatment group, patient ID, and assessment date/time.

"No patients qualify for this table" will be presented when there are no data available to report in a given table. A similar note will be presented for empty listings and figures.

If the result from the primary central lab of the 24-hour UPCR is missing, contains an inequality (eg, ≥6.1), or is reported as unable to process (UTP), the sample will be sent to a secondary central lab (eg, [redacted]) to be processed. This secondary central lab typically can produce the actual numerical value (eg, 6.1). Actual numerical values should be used instead of a stripped inequality value. A result using an inequality sign will only be used if no other actual numerical value is available; in this case, the inequality sign will be stripped from the value before use. The baseline value for 24-hour UPCR is defined as the average of the non-missing 24-hour UPCR results at Screening. Repeat test results on a different urine sample will not be used to replace non-missing original test data. When only one non-missing 24-hour UPCR result is available at Screening, then that single value will be used as baseline.

For all other parameters, the baseline value will be defined as the last non-missing evaluation prior to the first dose of study treatment (zetomipzomib or placebo), unless otherwise specified.

Study day will be calculated depending on the assessment date. When an assessment date is before the first dose of study treatment, the study day will be calculated as assessment date – first dose date. If the assessment takes place on or after the first dose of study treatment, the study day will be calculated as assessment date – first dose date + 1.

All instances where data may be imputed are detailed in this SAP; no other data imputations are planned. For by-visit summaries, patients will be counted only once for each planned visit. All scheduled and unscheduled assessments including the ETV will be mapped to a scheduled visit by study day according to the analysis visit windows specified in Table 2 (all study assessments except 24-hour urine) or Table 3 (24-hour urine only) below. The assessment used for the by-visit analysis will be selected as follows:

- If there is a corresponding scheduled visit within the analysis visit window, then data from the scheduled visit will be used for analysis. In the event of multiple corresponding scheduled visits, the visit closest to the scheduled day will be used. In the event of a tie, data from the earlier visit will be used.
- If there is no scheduled visit within the analysis visit window, then data from the visit closest to the scheduled day will be used for analysis. In the event of a tie, data from the earlier visit will be used.

If an assessment falls into an analysis visit window for a visit at which it was not planned to be collected per the protocol (see Appendix 1, Schedule of Assessments), the assessment will not be flagged for use in the by-visit analysis.

All assessments (scheduled, unscheduled, and ETV) will be included in the data listings.

Table 2: Analysis Visit Windows – All Study Assessments Except 24-hour Urine Collection

Visit	Target Day	Analysis Visit Window (Study Days)	Analysis Visit Name
Screening	-35 to -1	≤1	Baseline
Visit 1 / Week 1 (Day 1)	1		
Visit 2 / Week 2	8	2 to 19	Week 2
Visit 3 / Week 5	29	20 to 43	Week 5
Visit 4 / Week 9	57	44 to 71	Week 9
Visit 5 / Week 13	85	72 to 99	Week 13
Visit 6 / Week 17	113	100 to 127	Week 17
Visit 7 / Week 21	141	128 to 155	Week 21
Visit 8 / Week 25	169	156 to 183	Week 25
Visit 9 / Week 29	197	184 to 211	Week 29
Visit 10 / Week 33	225	212 to 239	Week 33
Visit 11 / Week 37	253	240 to 267	Week 37
Visit 12 / Week 41	281	268 to 295	Week 41

Visit	Target Day	Analysis Visit Window (Study Days)	Analysis Visit Name
Visit 13 / Week 45	309	296 to 323	Week 45
Visit 14 / Week 49	337	324 to 351	Week 49
Visit 15 / Week 53 (EOT)	365	352 to 379	Week 53
Visit 16 / Week 56 (EOS)	393	380 to 395	Week 56

EOS=End of Study; EOT=End of Treatment. Patients are not dosed at Week 53.

Table 3: Analysis Visit Windows – 24-hour Urine Collection Only

Visit	Target Day	Analysis Visit Window (Study Days)	Analysis Visit Name
Screening	-35 to -1	≤1	Baseline
Visit 5 / Week 13	85	72 to 113	Week 13
Visit 8 / Week 25	169	156 to 197	Week 25
Visit 11 / Week 37[a]	253	240 to 281	Week 37
Visit 15 / Week 53 (EOT)	365	352 to 379	Week 53
Visit 16 / Week 56 (EOS)	393	380 to 421	Week 56

EOS=End of Study; EOT=End of Treatment. Patients are not dosed at Week 53.

[a] Weeks 13, 25, 37 (primary endpoint), and 53 must use 24-hour urine sample; 2 consecutive FMV samples may not be used. Analysis Visit Window uses the same start day as the corresponding visit window in Table 2 and the end day is 4 weeks from target day. Per protocol Section 7.2.2, scheduled assessment may be postponed 14 days due to menstruation/infection and missing assessment can be replaced up to 4 weeks after missed collection date.

All statistical tests will be 2-sided, unless otherwise specified. No statistical comparisons will be performed between the two zetomipzomib dose groups.

All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.4 or higher.

4.1. Missing Start and Stop Dates

Prior/Concomitant Medications: MMF and Oral Corticosteroids Only

For protocol-required medications MMF and oral corticosteroids, partially missing medication start and stop dates prior to Screening will be imputed according to the following rules below. In general, partial start and stop dates once enrolled on study (ie, after Screening date) will not be imputed with exceptions noted below. Completely missing medication start and stop dates will not be imputed but will conservatively be identified as concomitant medications.

Partially missing start dates (where UK and UKN indicate unknown or missing day and month, respectively):

- UK-MMM-YYYY: If the month and year are ≤ the month and year of Screening date, assume 01-MMM-YYYY;
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is ≤ the year of Screening date, assume 01-JAN-YYYY.

Missing stop dates (where UK and UKN indicate unknown or missing day and month, respectively):

- UK-MMM-YYYY: If the month and year are < the month and year of Screening date, assume the last day of the month MMM YYYY. If the month and year are the same as the month and year of Screening date, assume the Screening date;
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is < the year of Screening date, assume 31 DEC YYYY. If the year is the same as the year of Screening date, assume the Screening date.

All Other Prior/Concomitant Medications

For all other prior and/or concomitant medications that are not required by the protocol, incomplete medication start and stop dates will be imputed according to the following rules below. Completely missing medication start and stop dates will not be imputed and will be included in summary tables as concomitant medications.

Missing start dates (where UK and UKN indicate unknown or missing day and month, respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study treatment, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study treatment month and year and the end date (after any imputation) is on or after the first dose of study treatment, then assume the date of the first dose of study treatment. If the month and year are the same as the first dose of study treatment month and year and the end date (after any imputation) is prior to the first dose of study treatment, then assume the end date for the start date;
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of the first dose of study treatment, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study treatment year and the end date (after any imputation) is on or after the first dose of study treatment, then assume the date of the first dose of study treatment. If the year is the same as the first dose of study treatment and the end date (after any imputation) is prior to the first dose of study treatment, then assume the end date for the start date.

Missing stop dates (where UK and UKN indicate unknown or missing day and month, respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

Any imputed stop date that is before the start date (known or imputed) will be set to the start date. Any imputed stop date that is after the date of death will be set to the date of death.

Adverse Events

Partially missing adverse event (AE) start dates will be imputed in a similar manner as other prior/concomitant medications above. Completely missing adverse event start dates will not be imputed and will be considered a TEAE. Completely or partially missing adverse event stop dates will not be imputed.

SLE Diagnosis Date and LN Diagnosis Date

Partially missing SLE diagnosis date and/or LN diagnosis date will be imputed as follows. UK and UKN indicate unknown or missing day and month, respectively:

- UK-MMM-YYYY: If the diagnosis month and year are different from the month and year of the Screening date, assume 15-MMM-YYYY. If the diagnosis month and year are the same as the Screening date month and year then assume 01-MMM-YYYY;
- DD-UKN-YYYY/UK-UKN-YYYY: If the diagnosis year is different from the year of the Screening date, assume 01-JUL-YYYY. If the diagnosis year is the same as the Screening date year, then assume 01-JAN-YYYY.

Completely missing SLE or LN diagnosis dates will not be imputed.

4.2. Sample Size

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 with the primary endpoint assessment and prior to the completion of the target study enrollment. Based on the IA findings, sample size (for patients with Class III/IV +/-V LN only) may be increased up to 50%; see Section 11.2 for details.

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.

Approximately 214 sites from ~21 countries worldwide are planned to participate in this study.

4.3. Analysis Sets

The following analysis populations are defined for this study.

4.3.1. Screen Failure Population

The Screen Failure (SF) Population is defined as the set of patients who consent to participate in the study but who are not subsequently randomly assigned to treatment. Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened once. Patients who failed Screening once but were subsequently rescreened and randomized will not be included in the SF Population. A patient is considered enrolled once the patient has been randomized to study treatment.

4.3.2. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population consists of all patients who are randomized to study treatment, regardless of whether they actually received study treatment. The ITT Population will be the primary analysis population used for the efficacy analyses. The ITT Population will be analyzed according to treatment as randomized.

4.3.3. Per Protocol Population

The Per-Protocol (PP) Population consists of all patients included in the ITT Population who have no study deviations that may substantially affect the efficacy results. Examples of study deviations that lead to PP exclusion include receiving a different study treatment than randomized or concomitant use of prohibited medication that would substantially affect the efficacy results. The final determination on study deviations, and thereby the composition of the PP Population, will be made in blinded fashion 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. The PP Population will be analyzed according to actual treatment received.

Additional details regarding the collection of study deviations and designation as significant/non-significant are presented in Section 5.2.

4.3.4. 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. The Safety Population will be analyzed by treatment group as actually received.

5. SUBJECT DISPOSITION

5.1. Disposition

Screen failures and reason for screen failure will be summarized and listed for the Screen Failure Population. For patients who failed Screening twice, only the most recent reason(s) for screen failure will be summarized. All screen failure data will be included in the data listing, with rescreening status clearly indicated.

The number and percentage of patients in each of the following categories will be summarized by treatment group and overall, separately for both the ITT and Safety Populations:

- Inclusion in each analysis population (ITT, PP, Safety)
- Ongoing on study treatment
- Completed study treatment
- Discontinued study treatment
  - Reason for discontinuation
- Ongoing on study
- Completed study
  - Week 37
  - Week 53
  - Week 56 (Safety follow-up; EOS)
- Terminated early from study
  - Reason for early termination

Patient disposition will be listed for the ITT Population.

In addition, the number and percentage of patients by region, country and investigational site will be summarized by treatment group and overall for the ITT Population. Regions/countries are as follows; the first digit of the corresponding site numbers in the electronic data capture system (EDC) are indicated in brackets:

- Europe, Middle East, and Africa (EMEA) [“1”]: Croatia, Greece, Portugal, Serbia, South Africa, Spain, United Kingdom
- Asia Pacific [“2”]: Australia, China, India, Republic of Korea, Malaysia, Philippines, Singapore, Taiwan (Province of China)
- North America [“3”]: United States
- Latin America [“4”]: Argentina, Brazil, Colombia, Guatemala, Peru

5.2. Study Deviations

All potential study deviations will be identified by the study team and indicated as either significant or non-significant in the Study Deviation Rules Document (SDRD). The severity of

each study deviation (ie, its impact on excluding the patient from one or more analysis populations) as initially assessed by the statistical team will also be indicated in the SDRD. Significant deviations are defined as important study deviations that affect the primary efficacy and/or safety assessments, the safety or mental integrity of a patient, or the scientific value of the study. Non-significant deviations are defined as study deviations that are identified but do not significantly impact the endpoints, safety or mental integrity of a patient, or the scientific value of the trial.

The significance and severity of each study deviation will be reviewed by the cross-functional study team on a regular basis during the course of the study; the SDRD is a living document and may be updated based on the findings of the ongoing team review. However, all severe study deviations leading to exclusion from the PP or other analysis populations must be reviewed and confirmed in a blinded manner at a Blinded Data Review Meeting held prior to the IA, primary analysis at Week 37, and final analysis/database lock at end of study.

The number and percentage of patients with at least one significant study deviation will be summarized by treatment group and overall for the ITT Population. Significant study deviations will be further summarized by deviation type (Protocol Deviation or ICH/GCP Deviation) and subtype.

All study deviations will be listed for the ITT Population, with significant and non-significant deviations clearly identified.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic information and baseline characteristics will be summarized by treatment group and overall for the ITT Population. They will also be listed for the ITT Population.

6.1. Demographics

The following demographic information will be presented:

- Age (years)
- Age group (≤30 years,>30 years)
- Sex at birth as integrated from RTSM (Male, Female)
- Is the patient of childbearing potential?
  - If Female at birth (Yes, No)
    - If No, summarize reason (Menopause ≥2 years, Hysterectomy, Bilateral oophorectomy, Non-therapy-induced amenorrhea ≥12 months, Bilateral salpingectomy)
  - If Male at birth (Not applicable)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Permitted)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Permitted, Other)
- Baseline weight (kg)
- Baseline height (cm)
- Baseline body mass index (BMI) (kg/m^2)

6.2. Baseline Disease Characteristics

The following baseline disease characteristics from the "Medical History – Systemic Lupus Erythematosus" eCRF page will be summarized by treatment group and overall for the ITT Population and the Safety Population.

- Time from SLE diagnosis to Screening (years)
  - Calculated as [(Screening date – SLE diagnosis date)/365.25]
  - Partial SLE diagnosis date will be imputed as specified in Section 4
- Time from LN diagnosis to Screening (years)
  - Calculated as [(Screening date – LN diagnosis date)/365.25]
  - Partial LN diagnosis date will be imputed as specified in Section 4
- Time from renal biopsy used for study inclusion to Screening (months)
  - If biopsy performed prior to Screening visit, calculate as [(Screening date – renal biopsy date)/30.44]
  - If biopsy performed during Screening period, set to 0

- Did patient have protocol-required chest x-ray (Yes, No)
  - If Yes:
    - When was chest x-ray performed (During Screening period, Within 90 days of IC)
    - Results (Normal; Abnormal, not clinically significant [NCS]; Abnormal, clinically significant [CS])
    - Did chest x-ray show evidence suggestive of active tuberculosis (TB) disease (Yes, No)
- LN class as integrated from RTSM (Class III/IV +/- V LN, pure Class V LN) – *stratification factor*
- LN classes: Class III only, Class IV only, Class III + V, Class IV + V, Class V only
- Lesions (Class III/IV)
  - Chronic only {should be screen failure; do not present category on table if n=0}
  - Active only
  - Active and chronic
  - Unknown
- Average 24-hour UPCR as integrated from RTSM (≤3.0, >3.0) – *stratification factor*
- 24-hour UPCR (mg/mg)
  - See Section 4 for derivation of baseline 24-hour UPCR
- eGFR value (mL/min/1.73m^2) (<60, ≥60)
- Treatment naïve (none or ≤3 months) (Yes, No)
- Number of prior LN flares (excluding the current flare)
- Treatment refractory (Yes, No, Not Available)
  - If Yes, summarize the number and percentage of patients with each applicable prior treatment
    - Cyclophosphamide
    - Mycophenolate/MMF
    - Tacrolimus
    - Voclosporin
    - Cyclosporin
    - Rituximab
    - Obinutuzumab
    - Belimumab
    - Anifrolumab
    - Leflunomide

  - Bortezomib
  - Eculizumab
  - IV immunoglobulin
  - Other
- IV methylprednisolone planned total dose as integrated from RTSM (0 to <500 mg, 500-1000 mg, or >1000 to 3000 mg) – *stratification factor*

The following additional baseline information will be similarly summarized for the ITT Population:

- Anti-dsDNA antibody (IU/mL)
- Categorical anti-dsDNA antibody
  - Positive (>24 IU/mL)
  - Negative (≤24IU/mL)
- C1q autoantibody (positive > 19 U or negative ≤ 19 U)
- Complement C3 (mg/dL)
- Complement C4 (mg/dL)
- Categorical complement (low C3, low C4, low C3 or low C4)
- Clinical lupus disease assessments
  - SLEDAI-2K Total Score
  - SLEDAI-2K positive for any of the following: Hematuria, Pyuria, or Casts
  - 28-Joint Count (both tenderness and swelling)
  - PGA
- EQ-5D-5L
  - Utility Index
  - EQ-VAS of general health

6.3. Medical History

General medical history will include all prior (ie, started before first dose of study treatment) medical conditions, complications, procedures, and surgeries not related to SLE as captured on the "Medical History" eCRF page. General medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 or higher.

The number and percentage of patients with any general medical history will be summarized overall and for each system organ class (SOC) and preferred term (PT) for the Safety and ITT Populations. SOCs will be presented in descending order of frequency overall and PTs and alphabetically in the event of ties. PTs within each SOC will be presented in descending order of frequency overall. At each level of summarization, patients will be counted once if they reported more than one event.

All general medical history data will be listed for the ITT Population.

6.4. Inclusion and Exclusion Criteria

Refer to Sections 4.2 and 4.3 of the study protocol for study inclusion/exclusion criteria.

Inclusion/exclusion criteria violations will be summarized by treatment group, type (inclusion or exclusion), and criterion. Criteria will be presented descending order of patient frequency overall, and criterion number (in case of ties). Only those inclusion/exclusion criteria that were violated by ≥1 patient will be included in the summary.

All inclusion/exclusion criteria violations will be listed for the ITT Population.

6.5. Other Background Information

6.5.1. European Alliance of Associations for Rheumatology/American College of Rheumatology Criteria for SLE

European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) criteria for SLE (Aringer et al., 2019) will be assessed at Screening. See Appendix 3 for a listing of EULAR/ACR criteria.

EULAR/ACR criteria will be listed for the ITT Population.

6.5.2. Infectious Disease Blood Tests

Screening blood tests for infectious diseases including TB, hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody, and human immunodeficiency virus (HIV) will be performed at the Screening visit only. Positive screens may require additional testing.

All results, other information related to infectious disease Screening, and country will be listed for the ITT Population.

6.5.3. Serum Pregnancy Test Results

Serum pregnancy test results at Screening will be listed for the ITT Population.

7. TREATMENTS AND MEDICATIONS

7.1. Prior and Concomitant Medications and Procedures

Prior and concomitant medications required by the protocol (ie, IV methylprednisolone, MMF or equivalent, and oral corticosteroids) will be identified directly on the eCRF. All other prior and concomitant medications (including all prescription medications, over-the-counter preparations, vitamins, and supplements) and procedures will be coded according to the World Health Organization drug dictionary WHODrug-Global-B3 Version 202309 or higher. Concomitant medications used in the study will be defined as medications used between the first dose date of investigational medicinal product (IMP) and through last follow-up visit. Prior medications will be defined as medications used and stopped prior to the first dose date of study treatment (ie, medications started before the first dose, not including the medications that continue during the study treatment).

Prior and concomitant medications and procedures will be summarized and listed as described below.

Rescue medications during the treatment period will be summarized and listed as described below.

See Section 4 for imputation of partially missing start/stop dates for prior and concomitant medications.

7.1.1. Protocol-Required Background Medications

7.1.1.1. IV Methylprednisolone

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 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. A total dose of IV methylprednisolone up to 3000 mg may be permitted.

Rescue use of IV methylprednisolone is collected directly on the eCRF. Any rescue use of IV methylprednisolone after the first dose of study treatment on Day 1 is considered a treatment failure. Treatment failures will be independently adjudicated by the CEC, in accordance with procedures documented in the CEC Charter.

All prior IV methylprednisolone use and concomitant use through the end of study will be collected on the "Prior and Concomitant IV Methylprednisolone" eCRF form. IV methylprednisolone use will be summarized separately for the following categories in both the ITT and Safety Populations:

- IV methylprednisolone use within 90 days prior to Screening
- IV methylprednisolone from IC date to Day 8
- Concomitant dosing of IV methylprednisolone as rescue therapy (Day 9 through EOS)
- Concomitant dosing of IV methylprednisolone not as rescue (Day 9 through EOS)

7.1.1.1.1. Prior to first dose of study treatment

The number and percentage of patients with any prior use of IV methylprednisolone and indication for use (eg, LN, SLE besides LN, Other) will be summarized by treatment group. Patients may be included in more than one indication category.

7.1.1.1.2. Day 1 (+/- 7 days)

- The following will be summarized by treatment group for Day 1 dosing: Number and percentage of patients in each IV methylprednisolone dosing category:
  - Planned total dose, as integrated from RTSM (0 to <500 mg, 500-1000 mg, or >1000 to 3000 mg) – *stratification factor*
  - Actual total dose received
    - 0, >0 to <500 mg, 500-1000 mg, >1000 to 3000 mg, >3000 mg
- Total dose received (mg), if >0
  - Overall
  - In patients weighing <45 kg
  - In patients weighing ≥45 kg

Protocol-required IV methylprednisolone dosing on Day 1 may actually occur on Day 1 (+/- 7 days). Protocol-required dosing can be identified by -7 ≤ dosing start day ≤ 8, indication = Lupus Nephritis, and rescue medication = No.

7.1.1.1.3. IC to Day 15

IV methylprednisolone dosing will also be summarized similarly for the time Period ranging from IC date to Day 15 of study.

- Total dose received (mg), if >0
  - Overall
  - In patients weighing <45 kg
  - In patients weighing ≥45 kg

7.1.1.1.4. Concomitant dosing as rescue therapy

The number and percentage of patients receiving concomitant IV methylprednisolone as rescue therapy and total dose received (mg) will be summarized by treatment group.

7.1.1.1.5. Concomitant dosing not as rescue therapy

The number and percentage of patients receiving concomitant IV methylprednisolone not as rescue therapy and total dose received (mg) will be summarized by treatment group.

All IV methylprednisolone use will also be presented in a single listing for the ITT Population, with prior use, protocol-required dosing on Day 1 (+/-7 days), dosing from IC date to Day 15, indication (LN, SLE besides LN, AE, Other), and any rescue therapy clearly identified.

7.1.1.2. Mycophenolate Mofetil (MMF)

All patients will receive daily MMF or equivalent ("MMF") for 52 weeks at a target dose of 2 g/day, in keeping with the standard of care. Doses from 1 g/day to 3 g/day are permitted with consultation of the Medical Monitor.

Patients already receiving MMF at Screening will 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.

Patients who are not receiving MMF at Screening will start MMF during the first week (after Week 1 dose of zetomipzomib or placebo) at 1 g/day and increase to 2 g/day during the second week (after Week 2 dose of zetomipzomib or placebo).

Changes to the patient's MMF dosing regimen are not permitted after Week 25, unless for tolerability issues (Protocol, Section 6.2.1.3). MMF or equivalent dose >2 g/day after Week 25 is considered a treatment failure. Treatment failures will also be independently adjudicated by the CEC, in accordance with procedures documented in the CEC Charter.

All prior MMF use and concomitant use through the end of study will be collected on the "Prior and Concomitant MMF or Equivalent Medications" eCRF form. MMF use will be summarized separately for prior and protocol-required concomitant dosing for both the ITT and Safety Populations.

Prior Use

The number and percentage of patients with any prior MMF use and type of medication used (MMF, MPA, MPS, Other) will be summarized by treatment group. Patients may be included in more than one medication type category.

Concomitant Use (protocol-required dosing)

The following will be summarized by treatment group:

- Number and percentage of patients currently receiving MMF at Screening* (Yes, No)
  - If Yes: Total daily dose at Screening (g/day)
- Average total daily dose (g/day) by study week (Day 1/Week 1 and Week 2 through Week 53)
- Number and percentage of patients with any total daily dose >2 g/day after Week 25 (study day 169)
- Number and percentage of patients with any total daily dose < 1g/day after Week 3 (study day 15)

**Use of MMF at Screening is defined as any use of MMF or equivalent within the 14-day period prior to Screening date.*

As needed, total daily dose as recorded on the eCRF will be converted to MMF equivalent in g/day directly within the EDC system. This derived value will be used for all MMF analyses. Details regarding the derivation are in Appendix 2.

A patient's MMF regimen may be daily, may vary by day(s) of the week (eg, higher dosage Monday-Friday and lower dosage Saturday-Sunday), or have another schedule (eg, every other day) during the course of the study. The eCRF will record the start/stop date and total daily dose associated with each unique regimen for each patient. The total daily dose for each day within the start/stop date interval, inclusive, will be determined based on the regimen. Days within a recorded start/stop date interval with no available dosing information will be assigned a dose of 0.

Total daily dose (g/day) on Day 1 (Week 1) will be summarized separately. For all other study weeks ≥2, average total daily dose (g/day) for Week X will be calculated as {[sum of total daily dose (g/day) over the 7-day period prior to Week X]/7}. The start and stop day (inclusive) of the 7-day period prior to Week X is defined below.

Start day of Week X: Day [(X – 1)*7 – 5]

Stop day of Week X: Day [(X – 1)*7 + 1]

Average total daily dose (g/day) will only be computed for Week X if there is an available dose value ≥0 for every day in the Week X calculation (ie, for all 7 days).

Average total daily dose (g/day) by week will be presented graphically by treatment group for the ITT Population.

- Average total daily dose of MMF from Day 1 through Week 53 (for patients who completed study treatment) and from Day 1 through EOT (for patients who terminated treatment early) will also be summarized by treatment group for the ITT Population.

All MMF or equivalent use will be listed for the ITT Population, with all prior use, protocol-required concomitant use, any concomitant doses <1 g/day or >3 g/day or any doses >2 g/day after Week 25 clearly identified.

7.1.1.3. Corticosteroids

All patients will receive daily oral corticosteroids (0.3 to 0.5 mg/kg/day, maximum of 40 mg/day) for 52 weeks.

For patients already receiving prednisone or equivalent ("prednisone") at a dose of 40 mg/day or higher at Screening, the dose will be tapered to ≤40 mg/day by Day 1 (Week 1). All patients will initiate prednisone tapering starting on Day 15 (Week 3) and should reduce the dose to ≤5 mg/day by Week 17. See the recommended tapering schedule in Table 2 of the study protocol.

Patients who exceed a dose greater than 10 mg/day prednisone for ≥3 consecutive days or for ≥7 days in total during the 8 weeks prior to the renal response assessment at Week 37 (ie, primary endpoint) will be considered a treatment failure.

All use of corticosteroids including topical use will be collected from at least 24 weeks prior to Screening and through the end of study on the "Prior and Concomitant Corticosteroid

Medications" eCRF form. Corticosteroid use will be summarized separately for prior use, protocol-required concomitant dosing, and other concomitant use for both the ITT and Safety Populations.

Prior Use

The number and percentage of patients will be summarized by treatment group for the following:

- Any prior use of corticosteroids (Yes, No)
  - If Yes:
    - Type of medication used (Betamethasone, Cortisone acetate, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone); patients may be included in more than medication type category
    - Indication for use (eg, LN, SLE besides LN, Other)

Patients may be included in more than one medication type and/or indication category.

Concomitant Use

The following will be summarized by treatment group:

- Number and percentage of patients receiving oral corticosteroids at Screening* (Yes, No)
  - If Yes: Total daily dose at Screening (mg/day)
- Average total daily dose (mg/day):
  - By study week (Day 1/Week 1 and Week 2 through Week 53)
  - By study week category (Weeks 1-2, Weeks 3-4, Weeks 5-6, Weeks 7-8, Weeks 9-12, Weeks 13-16, Week 17-20, Weeks 21-24, Weeks 25-28, etc.)
- Number and percentage of patients with >10 mg/day for ≥3 consecutive days or for ≥7 days in total during the 8 weeks prior to the renal response assessment at Week 37 (ie, primary endpoint)
- Number and percentage of patients with ≤ 10 mg/day for 8 weeks prior to the renal response assessment (eg. at Week 37 for the primary endpoint)
- Number and percentage of patients at Week 17 with ≤ 5 mg/day
- Number and percentage of patients at Week 17 with 0 mg/day
- Number and percentage of patients at Week 25 with ≤ 10 mg/day
- Average total daily dose of oral corticosteroids from Day 1 through Week 53 (for patients who completed study treatment)
- Average total daily dose of oral corticosteroids Day 1 through EOT (for patients who terminated treatment early)

**Use of oral corticosteroids at Screening is defined as any use of oral corticosteroids within the 14-day period prior to Screening date.*

As needed, total daily dose as recorded on the eCRF will be converted to prednisone equivalent in mg/day directly within the EDC system. This derived value will be used for all analyses of involving protocol-required oral corticosteroids. Details regarding the derivation are in Appendix 2.

A patient's oral corticosteroids regimen may be daily, may vary by day(s) of the week (eg, higher dosage Monday-Friday and lower dosage Saturday-Sunday), or have another schedule (eg, every other day) during the course of the study. The eCRF will record the start/stop date and total daily dose associated with each unique regimen for each patient. The total daily dose for each day within the start/stop date interval, inclusive, will be determined based on the regimen. Days within a recorded start/stop date interval with no available dosing information will be assigned a dose of 0.

Total daily dose (mg/day) on Day 1 (Week 1) will be summarized separately. For all other study weeks ≥2, average total daily dose (mg/day) for Week X will be calculated as {[sum of total daily dose (mg/day) over the 7-day period prior to Week X]/7}. The start and stop day (inclusive) of the 7-day period prior to Week X is defined below.

Start day of Week X: Day [(X – 1)*7 – 5]

Stop day of Week X: Day [(X – 1)*7 + 1]

Average total daily dose (g/day) will only be computed for Week X if there is an available dose value ≥0 for every day in the Week X calculation (ie, for all 7 days).

Average total daily dose (mg/day) by week will be presented graphically by treatment group for the ITT Population.

Other Concomitant Use (not protocol-required)

All other concomitant oral, intravenous, intramuscular, or intra-articular corticosteroid use not required by the study protocol will be summarized in a similar manner as prior use.

All corticosteroids use will be presented in a single listing for the ITT Population, with all prior use and protocol-required concomitant use clearly identified.

7.1.2. Prior and Concomitant SLE Medications

All prior and concomitant use of SLE medications will be collected from at least 24 weeks prior to Screening through the end of study using the "Prior and Concomitant SLE Medications" eCRF form and summarized separately by treatment group for both the ITT and Safety Populations.

The number and percentage of patients with any prior or concomitant SLE medication will be summarized overall and by each Anatomical Therapeutic Chemical (ATC) level 3 term and PT. ATC level 3 terms will be presented in descending order of frequency overall, and alphabetically in the event of ties. PTs within each ATC level 3 terms will be presented in alphabetical order. At each level of summarization, patients will be counted once if they reported more than one medication or therapy within the same PT or ATC level 3 term.

All prior and concomitant SLE medications will be presented in a single listing for the ITT Population, with indication (LN, SLE besides LN, Other: Specify) clearly identified.

7.1.3. Other Prior and Concomitant Medications and Therapies

All other prior and concomitant medications and therapies (ie, those not listed above) will be collected from 60 days prior to Screening through end of study using the "Prior and Concomitant Medications" eCRF form and summarized separately by treatment group for the Safety and ITT Population.

The number and percentage of patients with any other prior medication, concomitant medication or therapy will be summarized overall and by each ATC level 3 term and PT. ATC level 3 terms will be presented in descending order of frequency overall, and alphabetically in the event of ties. PTs within each ATC level 3 terms will be presented in alphabetical order. At each level of summarization, patients will be counted once if they reported more than one medication or therapy within the same PT or ATC level 3 term.

For other concomitant medications in this section, rescue use is collected directly on the eCRF and will be summarized.

Prohibited medications will be identified through blinded manual review by Kezar. Details regarding the manual review process are found in the separate CEC Charter. Prohibited concomitant medications will be summarized separately in a similar manner as other concomitant medications.

All other prior and concomitant medications and therapies will be presented in a single listing for the ITT Population, with prohibited and rescue medications clearly identified.

7.1.4. Concomitant Procedures

All concomitant procedures will be collected on the "Concomitant Procedures" eCRF form and summarized separately by treatment group for the ITT Population.

The number and percentage of patients with any concomitant procedure will be summarized overall and by each ATC level 3 term and PT. ATC level 3 terms will be presented in descending order of frequency overall, and alphabetically in the event of ties. PTs within each ATC level 3 terms will be presented in alphabetical order. At each level of summarization, patients will be counted once if they reported more than one concomitant procedure with the same PT or ATC level 3 term.

All concomitant procedures will be listed for the ITT Population.

7.2. Study Treatments

See Section 3.3 for details regarding study treatment.

7.2.1. Extent of Exposure

Extent of exposure to study treatment will be summarized by treatment group using descriptive statistics for the Safety analysis set:

- Number of injections administered
- Number of Injections (%) administered: In Clinic, At Home (Self, Caregiver, or Medical Professional)

- Categorical number of doses received (1-10, 11-20, 21-30, 31-40, 41-50, >50)
- Total cumulative dose received (mg)
  - Calculated as sum of dose received (mg) across all administered injections
- Average dose received (mg)
  - Calculated as (total cumulative dose received/number of administered injections)
- Duration of exposure (weeks), ignoring any treatment interruptions
  - Calculated as [(date of last dose – date of first dose + 1)/7]

All study treatment administration and exposure information, including at-home versus clinic administration, will be listed for the Safety Population. If applicable, a separate listing will be presented for study treatment exposure exceptions (study treatment not administered, full dose not administered, and/or study treatment not received as randomized).

7.2.2. Treatment Compliance and Modifications

The following treatment compliance and modification information will be summarized by treatment group using descriptive statistics for the Safety analysis set:

- Number and percentage of patients who:
  - Completed study treatment
  - Had at least one missed dose
  - Had at least one dose reduction (dose reduction only permitted in 60 mg treatment group per the protocol)
- Relative dose intensity (%)
  - Calculated as [(total cumulative dose received in mg/duration of exposure in days) / (total planned daily dose in mg/52)] * 100.
- Percent compliance with planned treatment regimen
  - Calculated as [(number of injections administered/52) * 100]
- Categorical percent compliance with planned treatment regimen (≤50%, >50-60%, >60-70%, >70-80%, >80-90%, >90-100%)

All compliance information will be listed for the Safety Population.

8. EFFICACY ANALYSIS

Unless otherwise specified, all efficacy analyses will be performed for the ITT Population with Class III/IV+/- V LN only. In general, all efficacy data will be summarized by treatment group and visit and listed for the ITT Population.

Unless specified otherwise, all efficacy analyses involving treatment comparisons will be performed separately for the following pairwise comparisons:

- zetomipzomib 60 mg versus pooled placebo
- zetomipzomib 30 mg versus pooled placebo

No statistical comparisons will be performed between the zetomipzomib high and low dose groups.

Unless otherwise specified, all statistical tests will be 2-sided at the 5% level of significance. As applicable, 2-sided 95% CIs will be presented. For hypothesis testing nominal p-values will be presented (Protocol, Section 10.6).

8.1. 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 patients in the ITT Population with Class III/IV+/- V LN only. 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

- CRR at Week 53
- PRR at Week 37
- PRR at Week 53
- CRR at Week 25
- 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 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 and 60 mg), respectively.

Each of the three pairwise comparisons above are assessed at the 2-sided α=0.05 level. As such, the overall Type 1 error rate across the three comparisons will become higher but controlled at the 2-sided level of 0.096716.

For each of the three pairwise comparisons above, a family-wise type 1 error rate at the α=0.05 level (2-sided) level will be used for the analysis of the primary and 5 key secondary endpoints 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 the 2 sided α=0.05 level. 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 the α=0.05 level for each of the pairwise comparisons. Results from all statistical analyses, regardless of the level of significance, will be provided. Results that are statistically significant according to the Hochberg method will be indicated with a "*" next to the significant p-value.

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.

Other (non-key) secondary and exploratory endpoints will be analyzed without controlling for the global family-wise type I error rate.

8.2. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who achieve CRR at Week 37. See Section 3.2.1 for details. CRR at Week 37 will be adjudicated by the CEC, in accordance with procedures documented in the CEC Charter. Both the adjudicated and original (non-adjudicated, as programmed) primary endpoint information will be retained on the analysis database, but the adjudicated endpoint will be used for the primary analysis.

To be a responder, a patient must complete the Week 37 visit and not be considered a treatment failure as defined in Section 3.2.1.

8.2.1. Intercurrent Events and Estimands

Table 4: Intercurrent Events

Label	Description
IE1	Treatment Failure as adjudicated by the CEC for any of the following criteria: • Prednisone or equivalent beyond that permitted (see Protocol Section 6.2.1.2); • MMF or equivalent >2 g/day after Week 25; • Requiring rescue therapy (see Protocol Section 6.2.3 for details); • Use of prohibited medications (see Protocol Section 6.2.4 and Protocol Section 13, Protocol Appendix 2 for details); • Discontinuation of zetomipzomib or placebo
IE2	Discontinuation of Study
IE3	Death

CEC=Clinical Endpoint Committee; IE=intercurrent event; MMF=mycophenolate mofetil.

Table 5: Estimands for Comparative Analysis between Zetomipzomib and Placebo (Part 1 of 2)

Objective	**Primary**: To evaluate the efficacy of zetomipzomib compared to placebo in the treatment of active LN	Same as primary	Same as primary
Estimand Label	Primary Estimand	Secondary Estimand	Tertiary Estimand
Estimand Description (*with Endpoint*)	Treatment difference (Zetomipzomib – Placebo) in proportion of patients achieving *CRR at Week 37*	Same as primary	Same as primary
Target Population	Patients in the ITT Population with confirmed Class III/IV +/- V LN	Patients in the ITT Population with confirmed Class III/IV +/- V or pure Class V LN	Patients in the Per Protocol Population with confirmed Class III/IV +/- V LN
Endpoint	CRR at Week 37	Same as primary	Same as primary
Estimator	Cochran-Mantel-Haenszel (CMH) test at 2 sided 5% level of significance, stratified by the randomization stratification factors	Same as primary	Same as primary

Objective	**Primary**: To evaluate the efficacy of zetomipzomib compared to placebo in the treatment of active LN	Same as primary	Same as primary
Estimand Label	Primary Estimand	Secondary Estimand	Tertiary Estimand
Treatment Conditions	Zetomipzomib 30mg vs. Pooled 30mg and 60mg Placebo and Zetomipzomib 60mg vs. Pooled 30mg and 60mg Placebo and [(Zetomipzomib 60mg + Zetomipzomib 30mg)/2] vs. Pooled 30mg and 60mg Placebo	Same as primary	Same as primary
Population-Level Summary	Difference in proportion of patients achieving CRR at Week 37 between patients assigned to zetomipzomib versus patients assigned to placebo, regardless of adherence in patients with confirmed Class III/IV +/- V LN	Difference in proportion of patients achieving CRR at Week 37 between patients assigned to zetomipzomib versus patients assigned to placebo, regardless of adherence in patients with confirmed Class III/IV +/- V or pure Class V LN	Difference in proportion of patients achieving CRR at Week 37 between patients treated with zetomipzomib versus patients treated with placebo who were strictly compliant with the protocol without major protocol deviations with confirmed Class III/IV +/- V LN
IE1 (TF)	Composite Method	Composite Method	Composite Method
IE2 (Discontinue Study)	Composite Method	Composite Method	Composite Method
IE3 (Death)	Composite Method	Composite Method	Composite Method
Missing Data Handling	NRI will be used to impute missing primary endpoint data due to any of the following prior to Week 37: early study discontinuation, lost to follow-up.	Same as primary	Same as primary

Objective	**Primary**: To evaluate the efficacy of zetomipzomib compared to placebo in the treatment of active LN	Same as primary	Same as primary
Estimand Label	Primary Estimand	Secondary Estimand	Tertiary Estimand
Rationale for Strategies	Estimand to assess all randomized patients in confirmed Class III/IV +/- V, regardless of actual treatment received and assigning non-response to primary endpoint for all IEs by using the composite method. This estimand maintains the benefits of randomization, ensuring that treatment groups remain comparable, and the study reflects real-world conditions.	To assess patients in the same manner of the primary estimand but in patients with confirmed Class III/IV +/- V or pure Class V LN.	To assess the patients that were strictly compliant with the protocol without major protocol deviations. This estimand most closely assesses the treatment effect under ideal or optimal conditions where the treatment is administered exactly as planned. This approach is useful for Clinical Relevance, Internal Validity, and Interpretability.

CRR=complete renal response; IE=intercurrent event; IMP=investigational medicinal product; ITT=intent-to-treat population; LN=lupus nephritis; NRI=non-responder imputation; TF=treatment failure.

Table 5: Estimand for Comparative Analysis between Zetomipzomib and Placebo (Part 2 of 2)

Objective	**Same as Primary**	**Same as primary**	**Same as primary**	**Same as primary**
Estimand Label	**Sensitivity 1 to Primary Estimand**	**Sensitivity 2 to Primary Estimand**	**Sensitivity 3 to Primary Estimand**	**Sensitivity 4 to Primary Estimand**
Estimand/Sensitivity Analysis Description (*with Endpoint*)	Treatment difference (Zetomipzomib – Placebo) in proportion of patients achieving *CRR at Week 37* as measured by logistic regression.	Treatment difference (Zetomipzomib – Placebo) in proportion of patients achieving *CRR at Week 37* regardless of intercurrent events IE1-IE3.	Treatment difference (Zetomipzomib – Placebo) in proportion of patients achieving *CRR at Week 37* in subset of population that did not require additional medication.	Treatment difference (Zetomipzomib – Placebo) in proportion of patients achieving *CRR at Week 37* in subset of population who completed treatment through Week 37.
Target Population	Same as primary	Patients in the ITT Population with confirmed Class III/IV +/- V LN that had intercurrent events IE1- IE4.	Subset of patients in the ITT Population with confirmed Class III/IV +/- V LN who did not require additional medication (including rescue therapy and protocol prohibited medications) or change in background medications prior to Week 37	Subset of patients in the ITT Population with confirmed Class III/IV +/- V LN who completed treatment through Week 37
Endpoint	Same as primary	Same as primary	Same as primary	Same as primary
Estimator	Logistic regression model will include study treatment, region, baseline UPCR, and the stratification factors	Same as primary	Same as primary	Same as primary
Treatment Conditions	Same as primary	Same as primary	Same as primary	Same as primary

Objective	**Same as Primary**	**Same as primary**	**Same as primary**	**Same as primary**
Estimand Label	**Sensitivity 1 to Primary Estimand**	**Sensitivity 2 to Primary Estimand**	**Sensitivity 3 to Primary Estimand**	**Sensitivity 4 to Primary Estimand**
Population-Level Summary	Difference in proportion of patients achieving CRR at Week 37 between patients assigned to zetomipzomib versus patients assigned to placebo, regardless of adherence in patients with confirmed Class III/IV +/- V LN, while correcting for baseline factors	Difference in proportion of patients achieving CRR at Week 37 between patients assigned to zetomipzomib versus patients assigned to placebo, regardless of adherence and regardless of having intercurrent events IE1-IE4 in patients with confirmed Class III/IV +/- V LN	Difference in proportion of patients achieving CRR at Week 37 between patients assigned to zetomipzomib versus patients assigned to placebo, regardless of adherence in patients with confirmed Class III/IV +/- V LN who did not require additional medication (including rescue therapy and protocol prohibited medications) or change in background medications prior to Week 37	Difference in proportion of patients achieving CRR at Week 37 between patients assigned to zetomipzomib versus patients assigned to placebo, regardless of adherence in patients with confirmed Class III/IV +/- V LN completed treatment through Week 37
IE1 (TF)	Composite	Treatment Policy	Principal Stratum	Composite
IE2 (Discontinue Study)	Composite	Treatment Policy	Principal Stratum	Composite
IE3 (Death)	Composite	Composite	Composite	Composite
Missing Data Handling	Same as primary	All available assessments will be used, regardless of intercurrent events (except Death). Missing data will not be imputed, instead a Tipping Point Analysis will be performed.	Same as primary	Same as primary

Objective	Same as Primary	Same as primary	Same as primary	Same as primary
Estimand Label	**Sensitivity 1 to Primary Estimand**	**Sensitivity 2 to Primary Estimand**	**Sensitivity 3 to Primary Estimand**	**Sensitivity 4 to Primary Estimand**
Rationale for Strategies	Sensitivity analysis to the primary estimand which assess all randomized patients in confirmed Class III/IV +/- V, regardless of actual treatment received and assigning non-response to primary endpoint for all IEs by using the composite method. This sensitivity analysis uses logistic regression to allow for controlling baseline covariates.	This sensitivity to the primary estimand will include patients that had intercurrent events (except Death) to reflect that these intercurrent events could occur in practice and thus can be considered as an inherent part of the treatment.	This sensitivity analysis to the primary estimand includes patients who did not require additional medication (including rescue therapy and protocol prohibited medications) or change in background medications prior to Week 37 and thus summarizes the effect in this population.	This sensitivity analysis to the primary estimand includes patients who completed treatment through Week 37 and thus summarizes the effect in this population.

CRR=complete renal response; IE=intercurrent event; IMP=investigational medicinal product; ITT=intent-to-treat population; LN=lupus nephritis; NRI=non-responder imputation; TF=treatment failure.

8.2.2. Primary Analysis

The primary analysis of the primary estimand will be conducted when all Class III/IV+/- V LN patients in the ITT Population reach (or would have reached) Week 37. Patients who experience an intercurrent event (IE) as specified in Table 4 above prior to the Week 37 visit will be considered non-responders (ie, will be imputed as not achieving CRR) by using the composite IE strategy. Patients with missing CRR assessment at Week 37 due to any other reason will also be considered non-responders through imputation in the missing data strategy.

The proportion of patients achieving CRR at Week 37 will be compared between zetomipzomib and placebo (separately for each of the two dose groups and the combined dose groups vs. pooled placebo) using the CMH test at 2-sided 5% level of significance, stratified by the randomization stratification factors specified in Section 3.5. The following statistics will be presented:

- Number and proportion of patients achieving CRR
- Weighted difference in CRR proportions
- Odds ratio and associated 2-sided 95% CI
- 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.

The CMH assumption of homogeneous treatment effect across strata will be tested using the Breslow-Day test. A significant Breslow-Day test (p-value <0.05) indicates that the treatment effect is not homogeneous across strata. Unstratified chi-square methods may also be used to analyze the primary estimand.

8.2.3. Sensitivity Analyses

8.2.3.1. Sensitivity Analyses to the Primary Estimand

The following sensitivity analyses which are described in detail in Table 5 will be performed for the primary estimand to assess treatment difference (Zetomipzomib – Placebo) in proportion of patients achieving CRR at Week 37:

- As measured by logistic regression
- Regardless of intercurrent events IE1-IE4
- In subset of population that did not require additional medication or change in background medication
- In subset of population who completed treatment through Week 37

The first sensitivity analysis of the primary estimand will be conducted in the ITT Population (Class III/IV +/- V patients only) will be estimated from the logistic regression model using the methodology described in Ge et al (Ge et al., 2011). The model will include covariates for treatment, stratification factors (LN Class, IV methylprednisolone), baseline 24-hour UPCR value (as a continuous number, not a stratification factor), and geographic region.

The secondary estimand is similar to the primary estimand, but estimates the difference in proportion of patients achieving CRR at Week 37 between patients assigned to zetomipzomib versus patients assigned to placebo, regardless of adherence in patients with confirmed Class III/IV +/- V or pure Class V LN.

8.2.3.2. Sensitivity Analysis using Multiple Imputation

Missing CRR assessments at Week 37 will be imputed using MI methods based on similar subjects with non-missing values at assumption of missing at random (MAR) and missing not at random (MNAR). First, missing values of composite CRR elements, UPCR and eGFR will be imputed separately, then missing CRR will be imputed based on the composite definitions in Section 3.2.1.

To implement multiple imputation of missing values of UPCR and eGFR, there will be two imputation steps carried out for each of these measures. First step, a Markov Chain Monte Carlo (MCMC) model imputes all intermediate missing values. Second step, a monotone regression model imputes remaining monotone missing values.

In the first step, the Markov Chain Monte Carlo (MCMC) models will be used with a single chain to impute missing values of UPCR or eGFR by treatment and stratification factor LN Class to create M=50 imputed datasets with monotone missing patterns. The seed will be set to 55218163 for these MCMC models. In the MCMC model for UPCR imputation, IV methylprednisolone planned total dose at baseline, UPCR values at baseline, Week 13, 25, 37, and 53 will be included as the model input variables. If this model does not converge, the

treatment may be included in the model as an input variable with dose (0, 30, and 60 mg). In the MCMC model for eGFR imputation, IV methylprednisolone planned total dose at baseline, UPCR baseline value, eGFR baseline value and all available post-baseline values up to Week 53 will be included as the model input variables. If there is a model convergence issue, the treatment may be included in the model with dose level (0, 30, 60 mg). If the convergence problem stays, reduction of eGFR post-baseline timepoints will be explored. In this exploration, exclusion of timepoints should be as minimum as possible and timepoints Week 13, 25, 37, and 53 must stay.

In the second step, monotone regression with the predictive mean matching (REGPMM) method will be used to impute the remaining missing values up on the output of 50 datasets with monotone missing patterns from the first step. In the REGPMM model for imputation of UPCR, treatment group and IV methylprednisolone planned total dose at baseline will be included in the model as classification variables. Baseline and post-baseline UPCR timepoints included in the first step imputation will be input variables as well. For eGFR imputation in this step, treatment group and randomization stratifications will be included in the model as classification variables and all timepoints included in the first step will be included in for the imputation of monotone missing. The seed will be set to 81635521.

CRR response at scheduled analysis visits through Week 53 will be defined following the definitions described in Section 3.2.1.

After the completion of imputation, the same statistical method as the primary analysis will be used to analyze each of the 50 complete datasets. The SAS® procedure MIANALYZE will be used to combine the results for the statistical inferences.

8.2.3.3. Sensitivity Analysis using Tipping Point

For the tipping point analyses, let M1 and M2 be the total number of patients with missing CRR assessment at Week 37 in the zetomipzomib and pooled placebo groups, respectively. There are overall (M1+1)*(M2 +1) possible ways for imputing missing data as responders or non-responders in this analysis, ranging from imputing all missing values as non-responders to imputing all missing values as responders in each of the two treatment groups. For each of the (M1+1)*(M2 +1) different imputation patterns, the same statistical method as the primary analysis will be used for testing statistical significance and the output will be plotted in a rectangle for inspection. The staircase region that separates significant and non-significant outcomes forms the tipping-point boundary.

8.2.3.4. Sensitivity Analysis using FMV-UPCR for missing 24-hour UPCR

Missing CRR and PRR assessments due to missing the 24-hour urine sample data, which is needed to calculate UPCR will be imputed using the calculated UPCR from 2 FMV urine samples for patients in the ITT Population. With this imputed data, the primary and key secondary endpoints will be analyzed and reported.

8.2.4. Subgroup Analysis

For each of the following subgroups, the proportion of patients in the ITT Population achieving CRR at Week 37 will be compared between zetomipzomib and placebo using the CMH test at 2-sided 5% level of significance. Non-responder imputation will be implemented as for the primary analysis in Section 8.2.2 and the same statistics will be presented.

- Average 24-hour UPCR at Screening visit (≤3.0 and >3.0) *{stratification factor}*
- LN Class (Class III/IV +/- V vs. pure Class V) *{stratification factor}*
- IV methylprednisolone on Day 1 +/- 7 days (0 to <500 mg, 500-1000 mg, or >1000 to 3000 mg) *{stratification factor}*
- Maximum MMF dose (≤2 g versus >2 g)
- Age group (≤30 years, >30 years)
- Sex at birth as integrated from RTSM (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Region (EMEA, Asia Pacific, North America, Latin America)
- 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 (III, III+V, IV, IV+V, Pure V)

If any subgroup contains <5 patients, inferential statistics will be suppressed.

8.3. Key Secondary Efficacy Endpoints

Key secondary endpoints include 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

Each key secondary endpoint will be analyzed using similar CMH methods as the primary, secondary, and tertiary estimands analyses for the 3 hypotheses stated in Section 8.1. IEs will be assessed through the time point of interest.

Sensitivity analysis 1 to primary estimand: Additionally, each key secondary endpoint will be analyzed using Ge, et. al (Ge et al., 2011) methods similar to the primary endpoint stated in Table 5.

8.4. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints will be analyzed for the ITT Population (Class III/IV +/- V).

8.4.1. Analysis of Continuous Secondary Efficacy Endpoints

Continuous secondary efficacy endpoints include:

- Percentage change from Baseline in UPCR by visit
- 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) index score and EQ-VAS of general health.

Observed values of the continuous secondary efficacy endpoints will be analyzed using the longitudinal data analysis method based on a mixed model for repeated measures (MMRM) approach. The model will include fixed effect terms for randomized treatment, visit, and randomized treatment by timepoint interaction. Baseline value will be included as a covariate and the randomization stratification factors will be included as class terms. Within subject error will be modeled by use of an unstructured variance-covariance matrix. If the model does not converge using the unstructured matrix (TYPE=UN), the following variance-covariance structures will be tried in this order until convergence is achieved: Toeplitz (TYPE=TOEP), compound symmetric (TYPE=CS).

Treatment effect (ie, the difference in least-square mean values between each zetomipzomib dose vs pooled placebo and the 2 zetomipzomib doses combined vs pooled placebo) estimates will be extracted from the model by visit along with the associated 95% CIs and 2-sided p-values.

8.4.2. Analysis of Time-to-Event Secondary Efficacy Endpoints

Time-to-event secondary efficacy endpoints include:

- Time to CRR
- Time to PRR
- Time to UPCR ≤0.5
- Time to death or renal-related events (see Section 3.2.1 for details regarding this endpoint)

For time-to-event endpoints, Kaplan-Meier methods will be used to estimate survival function, median survival time, and associated 95% CIs. The log-rank test (stratified for the randomization stratification factors) will be used to compare the two survival curves for each pairwise treatment comparison. Cox's proportional hazards model will be performed to assess differences between treatment groups. The model will include terms for treatment, stratification factors, and other select parameters including sex at birth, age, race, and baseline UPCR. Comparison of the survival distributions will use the score test for the hazard ratio from the Cox model.
All statistical tests will be 2-sided.

Censoring rules

- Patients who are randomized but not treated will be censored at Week 1 (study day 1).
- Patients who die due to any cause prior to completing treatment at Week 53 will be censored at the day of the last non-missing UPCR assessment prior to death
- Patients who discontinue early from the study will be censored at the day of discontinuation

- Patients who are still on-study but have incomplete follow-up at the time of analysis will be censored at the last contact date
- Patients who have completed study treatment and did not experience the defined event through Week 53 will be censored at Week 53 + 1 day

Survival curves will be presented graphically for each pairwise treatment comparison. For each treatment group of interest, the number of patients at risk by time, number of patients who met the endpoint, number of patients who were censored, and median time to meet the endpoint along with the associated 95% CI will be presented for each treatment group of interest. The hazard ratio and associated 95% CI, p-value from the score test of the hazard ratio, and p-value from the log-rank test will also be presented on the graph.

8.4.3. Analysis of Binary Secondary Efficacy Endpoints

Binary secondary efficacy endpoints include:

- 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

Binary secondary efficacy endpoints will be analyzed using similar CMH methods as the main analysis of the primary estimand.

8.5. Exploratory Endpoints

All exploratory efficacy endpoints will be analyzed for the ITT Population (Class III/IV +/- V). A subset of exploratory endpoints will be analyzed for the pure Class V LN patients as described in Section 8.5.3.

8.5.1. Analysis of Continuous Exploratory Endpoints

Continuous exploratory endpoints include:

- Change from Baseline in antibodies (anti-dsDNA antibody, C1q autoantibody)
- Change from Baseline in complement (C3, C4)
- 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 last visit in the GTI as measured by the GTI-CWS and the GTI-AIS
- Change from Baseline in SLEDAI-2K
- Change from Baseline in 28-joint counts (both tenderness and swelling counts)
- Change from Baseline in PGA score
- Change from Baseline in renal biopsy histopathology and immunohistopathology (optional; analysis of these endpoints is outside the scope of this SAP)
- Change from Baseline in IgM, IgG, and IgA

The continuous exploratory endpoints will be analyzed using similar MMRM methods as the main analysis of the continuous secondary efficacy endpoints. No MI analysis will be conducted for the continuous exploratory endpoints. Log-transformed values may be used for laboratory endpoints that are skewed and not normally distributed (eg, serum creatinine).

8.5.2. Analysis of Time-to-Event Exploratory Endpoints

Time-to-event exploratory endpoints include:

- Time to antibodies normalization or negative status (anti-dsDNA antibody normalization, anti-C1q antibody negative status)
- Time to complement (C3, C4) no longer being low
- Time to relapse or proteinuric flare
- Time to SLE Flare Index of severe, moderate, or mild

The time-to-event exploratory endpoints will be analyzed using similar Kaplan-Meier and log-rank test methods as the main analysis of the time-to-event secondary efficacy endpoints. Similar censoring rules will be followed as for the time-to-event secondary efficacy endpoints (see Section 8.4.2).

No graphs will be produced for the time-to-event exploratory endpoints.

8.5.3. Analysis of Binary Exploratory Endpoints

Binary exploratory endpoints include:

- 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 meet CRR by the China Center for Drug Evaluation (CDE) of NMPA Technical Requirements (Appendix 4), which is achieved if both of the following conditions are met:
  - urine protein quantification <0.5 g/24 h or urine protein/creatinine ratio (UPCR) <0.5 g/g;
  - eGFR reduction ≤10% of baseline or eGFR ≥90 mL/min/1.73 m^2.
- Proportion of patients who meet PRR by the CDE Technical Requirements definition (Appendix 4), which is achieved when both of the following conditions are met:
  - partial renal response can be regarded if urine protein quantification reduction ≥ 50% of baseline and <3.5 g/24 h, or UPCR reduction ≥ 50% of baseline and <3.0 g/g;

    and
  - eGFR reduction ≤ 10% of baseline or eGFR ≥90 mL/min/1.73 m^2.
- Proportion of patients who achieve urine protein quantification <0.5 g/24 h or urine protein/creatinine ratio (UPCR) <0.5 g/g and eGFR reduction ≤20% of baseline or eGFR ≥60 mL/min/1.73 m^2.
- Proportion of patients who achieve urine protein quantification <0.5 g/24 h or urine protein/creatinine ratio (UPCR) <0.5 g/g and eGFR reduction ≤15% of baseline or eGFR ≥60 mL/min/1.73 m^2.
- Proportion of patients who develop doubling of Baseline serum creatinine, kidney failure (receiving dialysis or kidney transplantation), or death
- Proportion of patients with Baseline SLEDAI-2K, excluding renal components, ≥6 with at least a 4-point improvement
- Proportion of patients with relapse or proteinuric flare
- Proportion of patients with SLE Flare Index of severe, moderate, or mild

The binary exploratory endpoints will be analyzed using similar CMH methods as the main analysis of the primary estimand.

8.5.4. Pure Class V Exploratory Endpoints

Exploratory endpoints in the pure Class V LN patients include:

- Proportion of patients that achieved CRR at Weeks 37 and 53
- Proportion of patients that achieved PRR at Weeks 37 and 53
- Change from Baseline in antibodies (anti-dsDNA antibody, C1q autoantibody)
- Change from Baseline in complement (C3, C4)
- 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 (LDL cholesterol, serum total cholesterol, serum triglycerides)
- Change from Baseline in IgM, IgG and IgA

These exploratory endpoints will be analyzed using similar methods as described in Section 8.5.1 and Section 8.5.3, as applicable.

8.5.5. Other Exploratory Endpoints

Other exploratory endpoints include:

- 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

Analysis of these endpoints is outside the scope of this SAP. See Section 8.6.2, Section 8.6.3, and Section 10 for additional information regarding these endpoints.

8.6. Biomarker Assessments

8.6.1. Cytokine Activity

Blood samples for assessment of cytokine activity and circulating leukocytes will be collected prior to study treatment administration at the visits specified in the Schedule of Assessments (Appendix 1).

Cytokine activity and circulating leukocytes will be summarized by treatment group and visit for the Safety Population.

All cytokine activity and circulating leukocyte data will be listed for the Safety Population.

8.6.2. Gene Expression/Pharmacogenomics

Blood samples for assessment of gene expression (RNA) profiling and genomic DNA genotyping will be collected prior to study treatment administration at the visits specified in the Schedule of Assessments (Appendix 1). These analyses are outside the scope of this SAP.

8.6.3. Urine Biomarkers

24-hour urine and urinalysis samples will be collected at the visits specified in the Schedule of Assessments (Appendix 1). A portion of these samples will be utilized by the central laboratory to identify urine biomarkers for response and/or safety.

Analyses of these samples are not included in this study and are outside the scope of this SAP.

8.7. Glucocorticoid Toxicity Index

The following continuous GTI scores will be summarized by treatment group (mean, standard deviation, median, interquartile range, minimum, maximum) and post-baseline visit for the ITT Population:

- GTI-CWS
  - Calculated as the sum of the maximum weighted scores for each of the 8 GTI domains from baseline through the visit of interest
  - The GTI-CWS can only increase or stay the same for the duration of the study
  - Lower GTI-CWS is associated with lower glucocorticoid toxicity over time
- GTI-AIS
  - Calculated as the sum of the weighted scores for each of the 8 GTI domains at the visit of interest
  - Lower GTI-AIS is associated with lower glucocorticoid toxicity over time

The 8 GTI domains will be listed for the ITT Population. Changes are with respect to the most recent previous on-study GTI assessment. Weighted scores for each category are noted in brackets below. More details can be found in the GTI Requirements Document (Appendix 5) and Weighting, Scoring and Analysis of the GTI (Appendix 6).

- Change in BMI
  - Decrease of ≥5 BMI units [-36]
  - Decrease of >2 to <5 BMI units [-21]
  - No significant change (+/- 2 BMI units) [0]
  - Increase of >2 to <5 BMI units [21]
  - Increase of ≥5 BMI units [36]
- Glucose metabolism
  - Improvement (decrease) in HbA1c AND decrease in use of glucose control medication [-44]
  - Improvement (decrease) in HbA1c OR decrease in use of glucose control medication [-32]
  - No significant change [0]
  - Increase in HbA1c OR increase in use of glucose control medication [32]
  - Increase in HbA1c AND increase in use of glucose control medication [44]
- Blood pressure (BP)
  - Improvement (decrease) in BP AND decrease in use of BP control medication [-44]

  - Improvement (decrease) in BP OR decrease in use of BP control medication [-19]
  - No significant change [0]
  - Increase in BP OR increase in use of BP control medication [19]
  - Increase in BP AND increase in use of BP control medication [44]
- Hyperlipidemia
  - Decrease in LDL AND decrease in use of lipid control medication [-30]
  - Decrease in LDL OR decrease in use of lipid control medication [-10]
  - No significant change [0]
  - Increase in LDL OR increase in use of lipid control medication [10]
  - Increase in LDL AND increase in use of lipid control medication [30]
- Steroid myopathy
  - Moderate weakness to none [-63]
  - Moderate to mild weakness [-54]
  - Mild weakness to none [-9]
  - No significant change [0]
  - None to mild weakness (without functional limitation) [9]
  - Mile to moderate weakness [54]
  - None to moderate weakness (with functional limitation) [63]
- Skin steroid-related toxicity
  - Decrease in skin toxicity – moderate to none [-26]
  - Decrease in skin toxicity – moderate to mild [-18]
  - Decrease in skin toxicity – mild to none [-8]
  - No significant change [0]
  - Increase in skin toxicity – none to mild [8]
  - Increase in skin toxicity – mild to moderate [18]
  - Increase in skin toxicity – none to moderate [26]
- Neuropsychiatric (NP) steroid-related symptoms
  - Decrease in NP toxicity – moderate to none [-74]
  - Decrease in NP toxicity – moderate to mild [-63]
  - Decrease in NP toxicity – mild to none [-11]
  - No significant change [0]
  - Increase in NP toxicity – none to mild [11]

  - Increase in NP toxicity – mild to moderate [63]
  - Increase in NP toxicity – none to moderate [74]
- Infection
  - No infection [0]
  - Oral/vaginal candidiasis or non-complicated zoster (< Grade 3) [19]
  - Grade 3, 4, or 5 infection [93]

9. SAFETY ANALYSIS

All summaries of safety will be performed for the Safety Population using descriptive statistics, unless otherwise noted. All safety data will be listed for the Safety Population.

Safety assessments will include AEs, clinical laboratory tests, vital sign measurements, physical examinations, weight, 12-lead electrocardiogram (ECG), urine pregnancy testing, and hepatitis B DNA assessments (for HBcAb-positive patients only).

9.1. Adverse Events

AEs from signing IC form through 30 days after last dose of study treatment will be recorded on the "Adverse Events" eCRF. 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).

In general, TEAEs will be summarized using cumulative incidence rates of TEAEs and exposure-adjusted incidence rates (EAIR) within each treatment group, and pairwise differences between zetomipzomib and placebo with point estimates and 95% CIs. Cumulative incidence rate is defined as the number of patients who experienced the specific event divided by the number of patients included in the analysis. Patients with multiple occurrences of the same event will be counted only once in the numerator. See Section 9.1.12 for details regarding EAIR.

Missing/partial AE start dates will be imputed as specified in Section 4. AEs will be coded using MedDRA Version 26.1 or higher. In general, summaries will be provided by treatment group, SOC and PT, and will provide both total number of events and number (percentage) of patients experiencing at least one event. SOCs will be presented in descending order of frequency overall, and alphabetically in the event of ties. PTs within each SOC will be presented in descending order of frequency. At each level of summarization, patients will be counted once if they reported more than one event within the same PT.

9.1.1. Incidence of Adverse Events

An overall summary table of AEs will present the number of patients with at least one event, the total number of events, and 95% CI (zetomipzomib – placebo) for the following:

- Any TEAE
- Any IMP-Related TEAE
- Any Grade 3 or 4 TEAEs
- Any Serious TEAE
- Any IMP-Related Serious TEAE
- AESI by the categories: Systemic Injection Reaction (SIR) and thrombotic microangiopathy (TMA) which also includes thrombotic thrombocytopenic Purpura (TTP) and hemolytic uremic syndrome (HUS)
- Any TEAE leading to Discontinuation from Study
- Any TEAE leading to study treatment Discontinuation

- Any TEAE leading to Dose Reduction
- Any TEAE leading to Dose Interruption
- Any TEAE Leading to Death

The number and percentage of patients with at least one TEAE will be summarized by treatment group (30 mg zetomipzomib, 30 mg Placebo, 60 mg zetomipzomib, 60 mg Placebo, 30mg and 60mg zetomipzomib, 30mg and 60mg Placebo) and overall (all patients).

All TEAEs will also be summarized by PT for each treatment group. PTs will be sorted in descending order of frequency in the combined zetomipzomib 30 mg and 60 mg group. A separate summary of the most common TEAEs (≥5% of patients in any treatment arm) will be presented in a similar manner.

All AEs will be summarized by PT only (without SOC) in descending order sorted by combined zetomipzomib 30 mg and 60 mg group

All AEs will be presented in a listing, with TEAEs clearly identified.

9.1.2. Relationship of Adverse Events to Study Drug

Adverse events will be classified as related to zetomipzomib or placebo or not related to zetomipzomib or placebo. Missing relationship status will be imputed as related.

The number and percentage of patients with at least one related TEAE will be summarized by treatment group and overall. Related TEAEs will be further summarized by SOC and PT.

9.1.3. Adverse Events by Maximum Severity

Severity of AEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 or higher. Grades are as follows:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Life-threatening
- Grade 5 = Fatal

The number and percentage of patients with TEAEs will be summarized by SOC, PT, and maximum severity for each treatment group Patients with multiple occurrences of the same event will be counted only once in the numerator, at the maximum severity. Missing severity will be imputed as severe (Grade 3).

9.1.4. Serious Adverse Events

The number and percentage of patients with at least one SAE will be summarized by treatment group and overall. SAEs will be further summarized by SOC and PT and by PT only in descending order. Missing serious status will not be imputed.

SAEs related to study treatment will be summarized separately by PT as follows:

- SAEs leading to death
- SAEs leading to study treatment withdrawal
- SAEs leading to Dose Reduction*
- SAEs leading to Dose Interruption

*Dose reduction due to AE is only permitted in the zetomipzomib or placebo 60 mg treatment group; no dose reduction is permitted in the 30 mg group.

All SAEs will be presented in a separate listing.

9.1.5. Adverse Events of Special Interest

The following adverse events of special interest (AESIs) have been identified in this study:

- Systemic injection reactions (SIRs)
- Thrombotic microangiopathy (TMA)

SIR events will be identified directly on the Adverse Events eCRF page. TMA events will be identified using the preferred terms “Thrombotic microangiopathy”, “Thrombocytopenic purpura”, or “Haemolytic uraemic syndrome”.

AESIs will be summarized in a stand-alone table for the Primary Analysis and the final analysis by SOC and PT. The number and percentage of patients with at least one AESI will be summarized by treatment group and overall. AESIs will be further summarized by SIR or TMA, PT.

Summaries will be presented for:

- AESIs related to IMP
- AESIs leading to dose reduction
- AESIs leading to early study treatment discontinuation
- Grade 1, 2, 3 and 4 AESIs
- AESIs by maximum severity

All AESIs will be presented in a separate listing.

9.1.6. Opportunistic Infections

Opportunistic infections of interest will be identified through blinded manual review by Kezar’s Medical Monitor.

Opportunistic infections in the STANDARDISED MedDRA QUERIES (SMQs) will be summarized in a stand-alone table for the Primary Analysis and the Final Data Analysis. The table will include all TEAEs identified as opportunistic infections using the following methods:

Step 1: The study programming team will pull out all TEAEs based on the SMQs of Opportunistic infections and produce an Excel spreadsheet with all TEAEs recorded up until the data cut.

Step 2: The study Medical Monitor and Safety Physician will review the TEAEs in the provided spreadsheet to determine whether each one of the pulled TEAEs will be considered an opportunistic infection. The criteria will be based on their medical judgement.

Step 3: The study Medical Monitor and Safety Physician will provide a list back to programming indicating which events should be flagged as an opportunistic infection.

Step 4: The data will be integrated into the ADAM data sets so that opportunistic infection tables and listings can be created.

The number and percentage of patients with at least one opportunistic infection will be summarized by treatment group and overall. Opportunistic infections will be summarized by SOC and PT in the following categories:

- Opportunistic infections related to IMP
- Opportunistic infections leading to dose reduction
- Opportunistic infections leading to dose interruptions
- Opportunistic infections leading to early treatment termination
- Grade 3 and 4 Opportunistic infections
- Opportunistic infections by maximum severity

All opportunistic infections will be presented in a separate listing.

9.1.7. Adverse Events Leading to Treatment Discontinuation

The number and percentage of patients with at least one TEAE leading to early discontinuation of study treatment will be summarized by treatment group and overall. TEAEs leading to early discontinuation of study treatment will be further summarized by SOC and PT.

TEAEs leading to discontinuation of study treatment will be presented in a separate listing.

9.1.8. Adverse Events Leading to Study Discontinuation

The number and percentage of patients with at least one TEAE leading to early study discontinuation will be summarized by treatment group and overall. TEAEs leading to early study discontinuation will be further summarized by SOC and PT.

TEAEs leading to study discontinuation will be presented in a separate listing.

9.1.9. Adverse Events Leading to Dose Reduction

Dose reduction due to AE is only permitted in the zetomipzomib or placebo 60 mg treatment group; no dose reduction is permitted in the 30 mg group.

The number and percentage of patients with at least one TEAE leading to dose reduction will be summarized by treatment group and overall. TEAEs leading to dose reduction will be further summarized by SOC and PT.

TEAEs leading to dose reduction will be presented in a separate listing.

9.1.10. Adverse Events Leading to Dose Interruption

The number and percentage of patients with at least one TEAE leading to dose interruption will be summarized by treatment group and overall. TEAEs leading to dose interruption will be further summarized by SOC and PT.

TEAEs leading to dose interruption will be presented in a separate listing.

9.1.11. Death

The number and percentage of patients with at least one TEAE leading to death will be summarized by treatment group and overall. TEAEs leading to death will be further summarized by SOC and PT.

TEAEs leading to death will be presented in a separate listing, to include cause of death and death certificate availability information.

Any outcome of death without a corresponding fatal TEAE will be presented in a separate listing, to include cause of death and death certificate availability information.

9.1.12. Exposure-Adjusted Incidence Rates

Exposure will be calculated within each treatment group as the total time at risk of the event across all patients. Exposure will be calculated differently depending on whether the subject did or did not experience the event in question. For patients who experienced the event, exposure is calculated as the number of days from the first dose of study treatment to the first occurrence of the event. For patients who did not experience the event, exposure is calculated as the number of days from first dose of study treatment to the end of study, inclusive. End of study is defined as the minimum of (treatment discontinuation date, treatment completion date, death date, lost to follow-up date).

The incidence rate (IR) for the given preferred term is calculated within treatment group as the number of patients (n) experiencing at least one occurrence of the event divided by the total time at risk for all patients in the treatment group. EAIR for the given preferred term will be computed as the number of events / 100 years of exposure. The difference (zetomipzomib – placebo) between EAIR along with a 95% CI for the difference will be reported separately for the zetomipzomib 30 mg and 60 mg dose groups using the normal approximation.

$$\text{EAIR} = \frac{n}{T} = \frac{n}{\sum t_i}$$

The test statistic is given by (z=zetomipzomib, p=placebo):

$$\text{E} = \left(\frac{n_z}{T_z} - \frac{n_p}{T_P}\right) / \sqrt{\frac{n_z}{T_z^2} + \frac{n_p}{T_p^2}}$$

The 95% CI for the difference in EAIR will be calculated as follows:

$$\left(\frac{n_z}{T_z} - \frac{n_p}{T_P}\right) - Z_{\alpha/2}\sqrt{\frac{n_z}{T_z^2} + \frac{n_p}{T_p^2}} \quad , \quad \left(\frac{n_z}{T_z} - \frac{n_p}{T_P}\right) + Z_{\alpha/2}\sqrt{\frac{n_z}{T_z^2} + \frac{n_p}{T_p^2}}$$

Summary tables presenting the number and percentage of patients, exposure time, EAIR, and treatment comparisons will be provided for the following:

- TEAEs, overall and by SOC and PT
- TEAEs ≥ Grade 3 by SOC and PT
- Serious TEAEs, overall and by SOC and PT
- TEAEs by severity grade with incidence of 5% and higher

9.2. Clinical Laboratory Evaluations

Clinical safety laboratory panels include hematology, serum chemistry, immunoglobulins (IgG, IgA, IgM), urinalysis, and coagulation. See Appendix 12 for a list of the clinical safety laboratory tests within each panel.

All clinical safety laboratory tests will be performed by the central laboratory according to the Schedule of Assessments (Appendix 1). Additional tests may be performed locally at any time during the study as determined necessary by the investigator; these data will be listed only and will not be included in summaries.

For continuous results, mean of the observed result, mean change from baseline (post-baseline visits only), and median change from baseline (post-baseline visits only) will be summarized for each scheduled visit. Standard deviation, median, interquartile range, minimum, and maximum will be presented. Additionally, last post-baseline value as well as maximum and minimum post-baseline values (through last safety follow-up visit and including unscheduled visits) and corresponding changes from baseline will be presented. For clinical laboratory measures that are not normally distributed per the Shapiro-Wilk test, the endpoint will be log-transformed when using MMRM methods or non-parametric test to assess change from baseline.

For qualitative results, the number and proportion of patients in each category will be summarized by scheduled visit.

As applicable, analysis of laboratory data will be based on SI units. For NCI-CTCAE gradable parameters, tables summarizing shift in NCI-CTCAE grades from baseline to each scheduled post-baseline timepoint, to last post-baseline assessment, and to worst post-baseline assessment (scheduled or unscheduled) will be displayed in cross-tabulations. For parameters with toxicity grading in both directions (high and low), shift will be presented separately for high and low.

For non-gradable parameters, tables summarizing shift in normal/abnormal classification from baseline to each scheduled post-baseline timepoint will be displayed in cross-tabulations. For parameters with normal/abnormal classification in both directions (high and low), shift will be presented separately for high and low.

For lab parameters, a graph of mean change from baseline (+/- SD) and/or median change from baseline (IQR) over time will be presented by treatment group.

All lab results will be listed by panel. Local lab results will be clearly identified on the listings.

9.2.1. Hematology

Hematology results will be summarized, plotted, and listed as applicable per Section 9.2.

9.2.2. Serum Chemistry

Serum chemistry results will be summarized, plotted, and listed as applicable per Section 9.2.

9.2.3. Urinalysis

Urinalysis results will be summarized, plotted, and listed as applicable per Section 9.2.

9.2.4. Coagulation

Coagulation results will be summarized, plotted, and listed as applicable per Section 9.2.

9.2.5. Immunoglobulins (IgG, IgA, IgM)

Immunoglobulin (IgG, IgA, IgM) results will be summarized, plotted, and listed as applicable per Section 9.2.

9.3. Vital Sign Measurements

Vital signs will be taken before blood collection (if applicable at the visit) and prior to zetomipzomib or placebo administration. A second set of vital signs will be obtained on the Day 1 (Week 1) visit 30 minutes (±15 minutes) after zetomipzomib or placebo has been administered.

The following vital sign assessments will be made according to the Schedule of Assessments (Appendix 1):

- Blood pressure (systolic and diastolic in mmHg)
- Pulse rate (beats/min)
- Respiratory rate (breaths/min)
- Body temperature (°C)
- Height (cm; collected at Screening visit only)
- Weight (kg; not collected at telehealth visits)
- BMI (kg/m^2)

Vital signs will be summarized using descriptive statistics by scheduled visit (and time point, if applicable) within each treatment group.

A graph of mean change from baseline (+/- SD) over time will be presented by treatment group for all vital signs.

All vital sign data will be listed.

9.4. Physical Examination

A full physical examination will be performed at Screening only. A symptom-directed brief physical examination will be performed at all other visits. Body systems assessed will include:

- General Appearance
- Head
- Eyes
- Ears
- Nose
- Throat
- Neck
- Dermatological
- Respiratory
- Cardiovascular
- Abdomen
- Extremities
- Neurological
- Musculoskeletal

The number and percentage of patients with the following findings for each body system will be summarized by treatment group:

- Normal
- Abnormal, NCS
- Abnormal, CS
- Not done

All physical examination data will be listed.

9.5. Electrocardiogram

A 12-lead ECG with QTcF interval will be performed at Screening, Week 25 (between 30 minutes to 4 hours post-dose), Week 53 (EOT) and the ETV, if applicable. The ECG will be performed prior to vital sign assessments and following 10 minutes of supine rest.

The following ECG parameters will be summarized by treatment group and visit:

- PR interval (msec)
- RR interval (msec)
- QRS duration (msec)
- QT interval (msec)

- QT interval, categorical (msec)
  - ≤500
  - >500
- QT interval, categorical change from baseline (msec)
  - ≤60
  - >60
- QTcF interval (QT interval with Fridericia's correction*; msec)
- QTcF interval, categorical (msec)
  - ≤450
  - >450 – ≤480
  - >480
- QTcF interval, categorical change from baseline (msec)
  - ≤30
  - >30 – ≤60
  - >60
- Overall ECG interpretations
  - Normal
  - Abnormal, NCS
  - Abnormal, CS
  - Not done

* *Fredericia Formula for QTcF interval = QT interval / (RR interval)$^{1/3}$. QTcF will be calculated by the site and recorded directly on the ECG eCRF page.*

All ECG data will be listed.

9.6. Other Safety Data

9.6.1. Urine Pregnancy Test Results and Outcomes

Urine pregnancy test results by visit as well as any pregnancy outcome information will be listed for all women of child-bearing potential in the Safety Population.

9.6.2. Hepatitis B DNA

Hepatitis B DNA assessments by visit will be listed for all HBcAb-positive patients who were permitted to enter the study and are in the Safety Population.

10. PHARMACOKINETICS

[redacted] will provide Study Data Tabulation Model (SDTM) serum study treatment concentration dataset (PC) to Kezar's third-party vendor. Serum study treatment concentration and population PK analysis datasets and associated analyses will be performed by Kezar's third-party vendor and are outside the scope of this SAP.

11. INTERIM ANALYSIS

An IA will be performed when approximately 50% of the randomized patients with Class III/IV +/-V LN have completed or would have completed the primary endpoint assessment at Week 37 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 patients with Class III/IV +/-V LN) if the CP for the primary analysis is ≥40% and <80%. The proportion of patients achieving CRR at Week 37 (the primary endpoint), the proportion of patients achieving PRR at Week 37, and mean percentage change from Baseline in UPCR at Week 37 will be evaluated using similar methods as specified in Section 8.2, Section 8.3, and Section 8.4.1. The study may not be stopped early for success based on the IA findings.

11.1. Futility Analysis

The futility boundary using the Lan-DeMets method (O'Brien and Fleming, 1979; DeMets and Gordon Lan, 2014) is non-binding and is shown in Table 6. The calculation was performed using [redacted] The futility boundary of Δ=5.4% (4.7% CP 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 by the Sponsor to stop the study for futility or to continue as planned will be reached after careful review of the data by the IDMC.

Table 6: 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% (CP at the observed value according to [redacted]=4.7%)

CP=conditional power; CRR=complete renal response; IA=interim analysis; LN=lupus nephritis.

11.2. Potential Sample Size Re-estimation

The (Mehta and Pocock, 2011) methods will be used for potential sample size re-estimation (SSR). The IA may result in a sample size increase of up to 50% (only for patients with Class III/IV +/-V LN) if CP is ≥40% and <80% (defined as the "promising zone"). Sample size can stay the same or increase based on the results of this analysis, but it cannot be decreased. Using these methods, the type I error rate will be preserved and will not be inflated. If conditional power is between 40% and 50% then the Cui, Hung, and Wang statistic (Cui et al., 1999) will be used for the final analysis to preserve type-I error rate.

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

CRR=complete renal response; LN=lupus nephritis

[a] The "promising zone". 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).

Calculations will be performed separately for both treatment comparisons (zetomipzomib 60 mg vs pooled placebo and zetomipzomib 30 mg vs pooled placebo) and the following SSR rules which are designed to ensure at least one treatment comparison will have 80% power will be applied in the following order based on IA results:

1. Do not increase planned sample size if CP is <40% and the futility stopping rule is not met for both treatment comparisons.
2. Do not increase planned sample size if CP ≥80% is met for at least one treatment comparison.
3. Increase sample size if 40% ≤ CP <80% for at least one of the two treatment comparisons. For the treatment comparison with the higher CP, the number of patients will be increased to the sample size needed to achieve CP of 80% or increased by 50%, whichever is smaller. The number of patients for the other treatment comparison will be increased by the same amount.

The conditional power is calculated assuming the observed effect size at the IA is the true effect size. The calculation is based on B-value (Lan and Wittes, 1988). Let D_1 denote the number of patients assessed for the primary endpoint at the IA and D_2 denote the total number of patients for the final comparison at end of study. The information fraction for the conditional power calculation is

$$t = D1/D2.$$

Let Z_t denote the quantile of the normal distribution associated with the CMH test statistic at the IA. The B-value at the IA is calculated as:

$$B(t) = Z_t\sqrt{t}$$

When data are monitored at t, B(t) is observed, and the conditional power assuming the trend indicated by the interim data is calculated as

$$CP_t = 1 - \Phi\left\{\frac{z_{0.975} - \frac{B(t)}{t}}{\sqrt{1-t}}\right\},$$

where $\Phi(\cdot)$ is the standard normal cumulative density function.

The exact formula for calculating sample size will not be available to the blinded team in order to prevent back-calculation of the treatment effect.

12. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An external IDMC will periodically review cumulative unblinded data to evaluate safety during the study. The IDMC will be convened regularly, at least twice a year, and *ad hoc* as needed. It is the responsibility of the IDMC to weigh the risks and benefits of study treatment throughout the duration of the trial, to include monitoring evidence for treatment harm (eg, toxicity, AEs, SAEs, and deaths) and requesting additional data analyses as necessary for the safety review process. The IDMC can recommend stopping the study for safety reasons based on their review and findings. IDMC recommendations will be provided to Kezar.

Details regarding the composition, scope, conduct, processes, and responsibilities of the IDMC are detailed in a separate IDMC Charter.

13. CHANGES IN THE PLANNED ANALYSIS

- Analysis of opportunistic infections has been added in the SAP, Section 9.1.6.
- In the Protocol Section 10.6, jump to placebo and tipping point imputation analyses are mentioned as a method for dealing with missing data in general. However, in the SAP, we have removed these analyses for non-key secondary endpoints.
- Respiratory rate has been added to this SAP because it was inadvertently omitted from the Protocol, but was routinely collected during conduct of the study.
- Clarification that "Time to UPCR ≤0.5" is considered a secondary efficacy study endpoint, as this is mentioned as a 'variable' in Protocol Section 10.6: "For time-to-event variables (eg, time to CRR, time to PRR, and time to UPCR ≤0.5), the Kaplan Meier method… ". This has been added to Table 1 in the SAP.
- The number of sites and countries has been updated in the SAP to "Approximately 214 sites from ~21 countries worldwide are planned to participate in this study" which differs from the number mentioned in the Protocol and is more accurate.
- Intercurrent events as defined in the Protocol (Table 6) were redefined and provided with clear labels in Section 8.2.1, for the purpose of the SAP. For example, non-responder events were combined under Treatment Failure (by definition) and Death was added.
- A Tertiary Estimand has been added to this SAP (for the PP Population) compared with the Protocol which called the analysis with the PP Population a 'supportive' analysis.
- Per Protocol, Section 10.6.1.1 states "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.". In the SAP, Section 8.2.1 , early study discontinuation, or lost to follow-up are being managed using the Estimand framework, see SAP, Table 5.
- The protocol Section 10.6.1, states: "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." However, in the SAP, Section 8.2.3.1 we specify that the baseline 24-hour UPCR value (as a continuous number) will be used instead of the categorical strata factor by stating: "The model will include covariates for treatment, stratification factors (LN Class, IV methylprednisolone), baseline 24-hour UPCR value (as a continuous number, not a stratification factor), and geographic region."

- Added 3 new exploratory endpoints to the SAP which were not included in the Protocol:
  - Time to antibodies normalization or negative status (anti-dsDNA antibody normalization, anti-C1q antibody negative status)
  - Time to complement (C3, C4) no longer being low
  - Change from Baseline in IgM, IgG, and IgA
- It should be noted that there is no reference to the sponsor's Steering Committee (SSC) in the SAP because Kezar has decided not to form and include a SSC in this study.
- The following analytes have been added to Table in Appendix 12:
  - neutrophil count
  - Anti-dsDNA
  - Complement (C3 and C4)
  - C1q autoantibody
  - Quantitative immunoglobulins (immunoglobulins M, G, and A)
  - white blood cells
  - red blood cells
  - 24-hour UPCR
  - FMV UPCR
  - 24-hour Proteinuria (Urine Protein (24hr))

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15. APPENDICES

APPENDIX 1. 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 Sections 6.2.1 and 6.2.2 of the study protocol.

[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.

APPENDIX 2. MMF AND ORAL CORTICOSTEROID CONVERSION

MMF

Step 1 – If recorded in mg or ug on eCRF, convert to g.

Step 2 – For MPA or MPS, multiply by conversion factor 1.3888 to get Total Daily Dose (g) in MMF equivalent. Conversion factor is calculated as 1/0.720.

Example: 720mg MPA x 0.001 g/mg x 1.3888 = 1g MMF.

Oral Corticosteroids

Corticosteroid	Protocol Table 1
Prednisone	20
Betamethasone	2.4
Cortisone acetate	100
Dexamethasone	3
Hydrocortisone	80
Methylprednisolone	16
Prednisolone	20

Step 1 – If recorded in g on eCRF, convert to mg (multiply by 1000).

Step 2 – Multiply by appropriate conversion factor to get Total Daily Dose (mg) in prednisone equivalent. Conversion factor is calculated as 20/(protocol Table 1 value) to get equivalent of 1 mg prednisone.

Corticosteroid	Conversion factor based on protocol Table 1
Prednisone	1
Betamethasone	8.3333
Cortisone acetate	0.2
Dexamethasone	6.6667
Hydrocortisone	0.25
Methylprednisolone	1.25
Prednisolone	1

Example: 80 mg hydrocortisone x 0.25 = 20 mg prednisone equivalent

APPENDIX 3. AMERICAN COLLEGE OF RHEUMATOLOGY (ACR) / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY (EULAR) CRITERIA

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended
Fever	Temperature >38.3°C
Leukopenia	White blood cell count <4,000/mm³
Thrombocytopenia	Platelet count <100,000/mm³
Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, AND positive Coombs' (direct antiglobulin) test
Delirium	Characterized by 1) change in consciousness or level of arousal with reduced ability to focus, 2) symptom development over hours to <2 days, 3) symptom fluctuation throughout the day, 4) either 4a) acute/subacute change in cognition (e.g., memory deficit or disorientation), or 4b) change in behavior, mood, or affect (e.g., restlessness, reversal of sleep/wake cycle)
Psychosis	Characterized by 1) delusions and/or hallucinations without insight and 2) absence of delirium
Seizure	Primary generalized seizure or partial/focal seizure
Non-scarring alopecia	Non-scarring alopecia observed by a clinician†
Oral ulcers	Oral ulcers observed by a clinician†
Subacute cutaneous OR discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician:† Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted). OR Discoid lupus erythematosus observed by a clinician:† Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition may be noted)
Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician† If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course)
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of 1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), 2) pericardial rub, 3) EKG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI)
Joint involvement	EITHER 1) synovitis involving 2 or more joints characterized by swelling or effusion OR 2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class II: Mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy Class V: Membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations

Class III or IV lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class III: Focal lupus nephritis: active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations Class IV: Diffuse lupus nephritis: active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or >the 99th percentile) or positive anti-β_2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal
Anti-dsDNA antibodies OR anti-Sm antibodies	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies

* SLE = systemic lupus erythematosus; LDH = lactate dehydrogenase; CT = computed tomography; MRI = magnetic resonance imaging; EKG = electrocardiography; ISN = International Society of Nephrology; RPS = Renal Pathology Society; anti-β_2GPI = anti–β_2-glycoprotein I; anti-dsDNA = anti–double-stranded DNA.
† This may include physical examination or review of a photograph.

APPENDIX 4. TECHNICAL GUIDELINE ON CLINICAL TRIALS OF DRUGS FOR LUPUS NEPHRITIS TREATMENT

Technical Guideline on Clinical Trials of Drugs for Lupus Nephritis Treatment

September 2023

Technical Guideline on Clinical Trials of Drugs for Lupus Nephritis Treatment

I. Introduction

(I) Characteristics of the disease

Lupus nephritis (LN) refers to renal impairment caused by systemic lupus erythematosus (SLE).

With a prevalence of 30.13-70.41/100,000, SLE is the most common systemic autoimmune disease in China. Kidneys are the most frequently affected organs in SLE, and 40%-60% of SLE patients have LN at the beginning of SLE. LN is the most common secondary immune glomerular disease in China and prone to flare (flare rate is 33%-40%). In China, the 10-year renal survival rate in LN is 81%-98%. LN is one of the common causes of end-stage kidney disease (ESKD) and also an important cause of death of SLE patients.

The goal of LN treatment is to protect kidneys, prevent or delay the deterioration of renal function, reduce the incidence rate and mortality of chronic kidney disease (CKD) and renal failure, and reduce drug-related toxicity.

LN treatment usually includes two phases, ie, induction and maintenance. Individualized treatment regimens should be selected based mainly on disease activity, pathological types of kidneys and treatment responses. Few drugs have been approved for LN treatment; additionally, their efficacy is limited, and certain safety problems exist.

(II) Purpose and scope

This guideline aims to provide technical guidance on clinical trials of drugs for LN treatment. This guideline is applicable to the development of chemical drugs and therapeutic biologics. It is used as a recommendatory document. When applying this guideline, please refer also to Good Clinical Practice (GCP), the International Council for Harmonization of Technical Requires for Pharmaceuticals for Human Use (ICH) guidelines, and other relevant guidelines that have been released at home and abroad. This guideline only represents the current views and perceptions of drug regulatory authorities and does not have mandatory legal binding. With the progress of scientific research, this guideline will be constantly improved and updated.

II. General considerations

Overall design of the clinical trial shall depend on the characteristics of drugs, the development goal and objectives of the clinical trial for comprehensive consideration.

(I) Study population

Clinical trials assessing renal outcomes should include patients with active lupus nephritis. Diagnosis of lupus nephritis should be in accordance with the latest generally accepted criteria. SLE disease activity and LN impairment should be documented in detail, including changes in proteinuria, active urinary sediment, and renal function.

Classification should be performed by pathological assessment of renal biopsy to identify pathological types of kidneys. It is recommended to use the 2018ISN/RPS revised criteria and characterize the pathological activity of kidneys and chronicity in LN with activity index (AI) and chronicity index (CI). Renal biopsy should be performed as close as the initiation of study treatment, preferably within 6 months prior to randomization. Combinations of different pathological types of nephropathy may occur, including some special changes in the kidney, eg,

renal tubulointerstitial disease, vascular involvements (eg, lupus thrombotic microangiopathy), and lupus podocytosis, which should all be appropriately assessed.

Considering the impact of baseline levels on efficacy evaluation, stratification may be performed at randomization (eg, histology of lupus nephritis, level of proteinuria, and/or glomerular filtration rate [GFR], etc.). Concomitant medications or other relevant factors that could affect renal outcomes should be documented and taken into consideration in the trial design and analysis of results.

(II) Efficacy measures

Clinical trials of drugs for LN treatment are intended to assess drug efficacy and safety, including clinically significant improvement, eg, improving the estimated or measured glomerular filtration rate (eGFR or mGFR), reducing renal injury, slowing CKD progression, preventing recurrence etc. However, in view of the complexity of LN, measurement of disease activity by a single index alone is considered insufficient to fully reflect the therapeutic effect in individual patients. It is recommended to assess the disease activity through validated composite indices. Currently recommended efficacy indices include complete renal response rate, partial renal response rate, global activity of SLE (SLEDAI or BILAG scale), active urinary sediment, proteinuria, change in serum creatinine and GFR values etc.

Complete renal response should represent clinically significant improvement in renal function. For example, complete renal response can be regarded if both of the following conditions are met: ① urine protein quantification <0.5 g/24 h or urine protein/creatinine ratio (UPCR) <0.5 g/g; ② eGFR reduction ≤10%~15% of baseline or eGFR ≥90 mL/min/1.73 m^2.

Partial renal response represents clinical improvement in renal function, which can maintain GFR within the predefined limit relative to baseline but does not fulfill the criteria for complete response. For example, partial renal response can be regarded if both of the following conditions are met: ① urine protein quantification reduction ≥ 50% of baseline and <3.5 g/24 h, or UPCR reduction ≥ 50% of baseline and <3.0 g/g; ② eGFR reduction ≤ 10%~15% of baseline or eGFR ≥90 mL/min/1.73 m^2.

Attention should be paid to patient reported outcomes, and validated scales are recommended to assess physical, psychological, and social effects, such as 36-Item Short Form Health Survey (SF-36), Fatigue Severity Scale (FSS), FACIT fatigue scale or Brief Fatigue Inventory (BFI) etc.

(III) Other considerations

In case of novel designs such as adaptive design or any content not specified herein, prior communication with the drug regulatory authority is recommended.

In multi-regional clinical trials, consideration should be given to the potential impact of differences in disease characteristics, drug pharmacokinetics/pharmacodynamics (PK/PD) profiles and clinical practices on ethnic sensitivity evaluation. Entry into global development in the early phase is recommended to obtain PK, PD or PK/PD, efficacy and safety data in the Chinese patient population.

III. Clinical pharmacology studies

Clinical pharmacology should be investigated throughout drug clinical trials. Depending on drug characteristics, clinical pharmacology trial protocols should be designed for suitable populations

with reference to relevant guidelines, with consideration given to specific populations (eg, hepatic/renal insufficiency, the elderly, children, etc.).

The dose-exposure-effect relationship of drugs should be fully characterized, and the safety of drugs should be understood to provide basis for selection of appropriate dose regimens and dose modifications in subsequent clinical trials. Where biologics are involved, consideration should be given to the impact of drug immunogenicity on safety and efficacy.

IV. Exploratory clinical trials

Multi-center, randomized, double-blind and placebo parallel controlled design where the placebo is given in add-on to standard of care is recommended.

Based on previous PK/PD study results, multiple dose groups may be set to explore dose-response relationships of drugs. For drugs being investigated in 2 or more autoimmune diseases extrapolation of dose-finding across indications could be acceptable subject to adequate justification.

Duration of the study depends on the lupus patient profile (eg, severity of renal impairment), effect of the drug, study objectives and the corresponding endpoints.

For efficacy measures, the section regarding confirmatory clinical trials may be referred to.

Necessary drug-drug interaction studies should be conducted as early as possible to evaluate the effects of possible concomitant drugs used in clinical practices (eg, glucocorticoids, immunosuppressants) on efficacy and safety and to support the proposed concomitant medication design in confirmatory studies.

V. Confirmatory clinical trials

(I) Overall design

Multi-center, randomized, double-blind and parallel controlled design is recommended. The duration of confirmatory clinical trials is long, and studies should be conducted on the basis of standard of care. Superiority trial design against an active comparator or placebo is preferred. Non-inferiority studies could only be accepted provided that the selected comparator could be justified on the basis of a well-established efficacy, and an appropriately justified non-inferiority margin could be predefined. Such comparative studies must have assay sensitivity. For add-on trials, superiority design is recommended.

(II) Selection of controls

Placebo-controlled trials aim to evaluate the absolute efficacy of test drugs. Active-controlled studies aim to demonstrate the test drugs are superior or non-inferior to the control drugs. Subject populations for different clinical trials may differ in disease severity, disease progression risk and endpoints for efficacy assessment. Appropriate control drugs should be selected depending on the goal of drug development.

(III) Subjects

Specific inclusion/exclusion criteria should be developed depending on proposed indications and development goals. Inclusion of clinically active and biopsy-confirmed LN patients is recommended. The disease severity (including clinical indices and pathological changes) and prior medications should be evaluated.

(IV) Duration of therapy

LN is a chronic disease that require long-term drug therapy. In clinical trials on LN, the efficacy and safety of drugs in inducing response and maintaining therapeutic effects should be comprehensively evaluated. The minimum optimal duration should be 3 to 6 months for induction of partial response. At least 1 year might be needed for induction of complete renal response. For drugs for both induction and maintenance, an additional 1 year is required to observe maintenance of treatment effect after achieving a response. For clinical trials studying only the maintenance of treatment effects, the duration of treatment should be at least 1 year. Tapering the immunosuppressants after induction and/or maintenance period should be predefined and assessed thoroughly during the trial (if applicable).

(V) Efficacy measures

Clinical efficacy measures should be set based on the mechanisms of action of new drugs, therapeutic goals and study objectives.

1. Primary efficacy measures

1.1 Induction of complete renal response: assessment of the treatment effect of induction therapy, ie, the proportion of subjects achieving the criteria for complete renal response.

Partial renal response could only be accepted as primary endpoint if prospectively defined and relevance is well justified. For such situations, communication with the regulatory authority is recommended. If partial renal response is defined as the primary endpoint, complete renal response should be defined as a key secondary endpoint.

1.2 Maintenance of complete renal response and/or prevention of LN flares: assessment of the treatment effect of long-term maintenance therapy, ie, treatment effect in maintaining complete renal response and preventing LN flares (in terms of both incidence and severity).

1.3 Prevention of long-term damage and slowing CKD progression. The purpose is to slow GFR reduction, delay the occurrence of ESKD and primary complications (such as cardiovascular diseases). For efficacy measures, it is recommended relevant guidelines be consulted.

2. Secondary efficacy measures

Proportion of subjects achieving the criteria for partial renal response.

The changes of laboratory indices showing either activity of the renal disease or chronic damage, such as active urinary sediment, proteinuria and renal function, including serum creatinine and GFR values.

Assessment of whether reduction of doses of glucocorticoids and/or immunosuppressants is favored.

Clinical indices of SLE: presence of SLE manifestations, assessment of overall SLE activity.

Where possible, repeated renal biopsies after treatment for 6 months are recommended to assess changes in renal pathology (eg, activity and chronicity indices).

Long term renal outcomes: development of ESKD with requirement of chronic renal replacement therapy and/or transplantation.

(VI) Concomitant treatment

During drug clinical trials, changes in dosages and administration of concomitant drugs can affect the treatment effect of the study treatment. Therefore, concomitant treatment should be standardized and kept stable and balanced among groups as far as possible. If modifications of concomitant drugs (eg, ACEI or ARB) may be made during the clinical trial, corresponding regimens should be predefined in the clinical trial protocol.

(VII) Rescue therapy

With regard to the potential risk of disease exacerbation, the rescue therapy criteria and rescue therapy drugs should be predefined in the protocol to ensure the safety of subjects in clinical trials. The estimand should be defined for rescue therapy, which is regarded as an intercurrent event. For specific requirements, refer to E9R1.

VI. Safety evaluation

In principle, the common standards for safety evaluation should be followed.

(I) Specific adverse events to be monitored

Considering that the risks of infection, cardiovascular events and malignancies are greater in SLE patients, such events should be specifically monitored. Given that the kidney is an important target organ for SLE and patients with SLE often have concomitant renal impairment, potential impact of the new agent on renal function or, in turn, any influence of renal impairment on drug elimination should be adequately monitored. Adverse events related to common organs/systems involved in SLE should also be closely monitored. Long term follow-up data must be available.

(II) Long-term safety

LN is a chronic disease, and most drugs will need to be administered on a long-term basis. Therefore, sufficient exposures and exposure duration are required for safety observation. Reference to ICH E1 is recommended. Setting of an Independent Data Monitoring Committee in long-term trials is recommended. In clinical trials on LN, special consideration should be given to the following safety evaluation items:

1. Drugs for LN treatment typically exert influence on the immune system. Special attention should be paid to the possibility of risks of developing serious infections and malignancies.

2. For biologics, consideration should be given to immunogenicity and whether anti-drug antibodies developed due to immunogenicity affect the long-term efficacy and safety of the drug. Concomitant use of immunosuppressants may reduce the ability to detect immunogenicity, so special attention should be paid to concomitant medications in safety evaluation.

3. For further identification of rare adverse events associated with new drugs, intensive safety evaluation during randomized trials might contribute but long-term follow-up in a large population will be needed.

VII. References

[1] EMA, Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis. 26 February 2015.

[2] Chinese Guidelines for the Diagnosis and Treatment of Lupus Nephritis Drafting Group. Chinese guidelines for the diagnosis and treatment of lupus nephritis [J]. Med J China, 2019, 99 (44): 3411-3455.

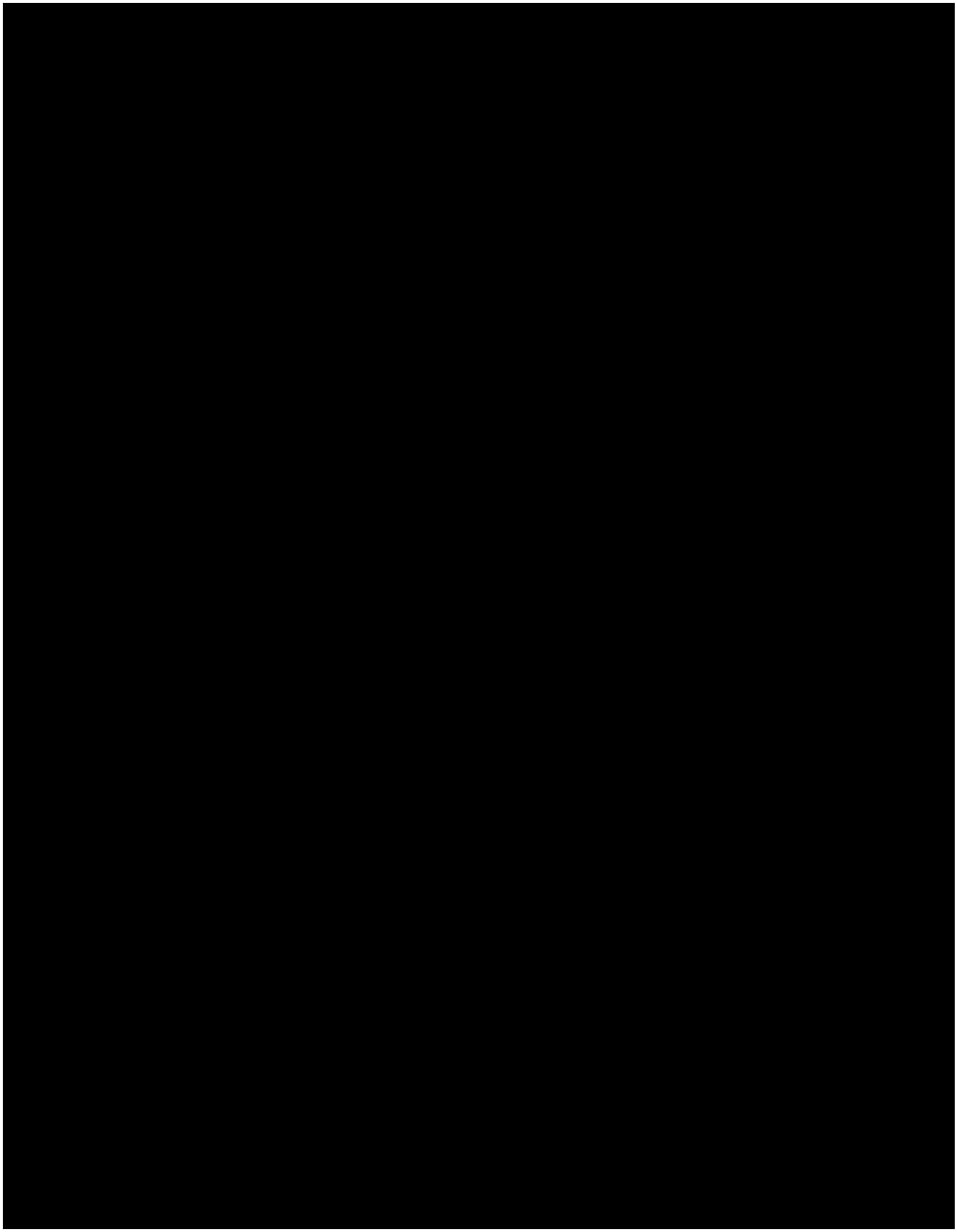
[3] Chinese Society of Rheumatology, Chinese Medical Association. Diagnosis and Treatment Standard of Lupus Nephritis. Chin J Intern Med, 2021, 60(9): 784-790.

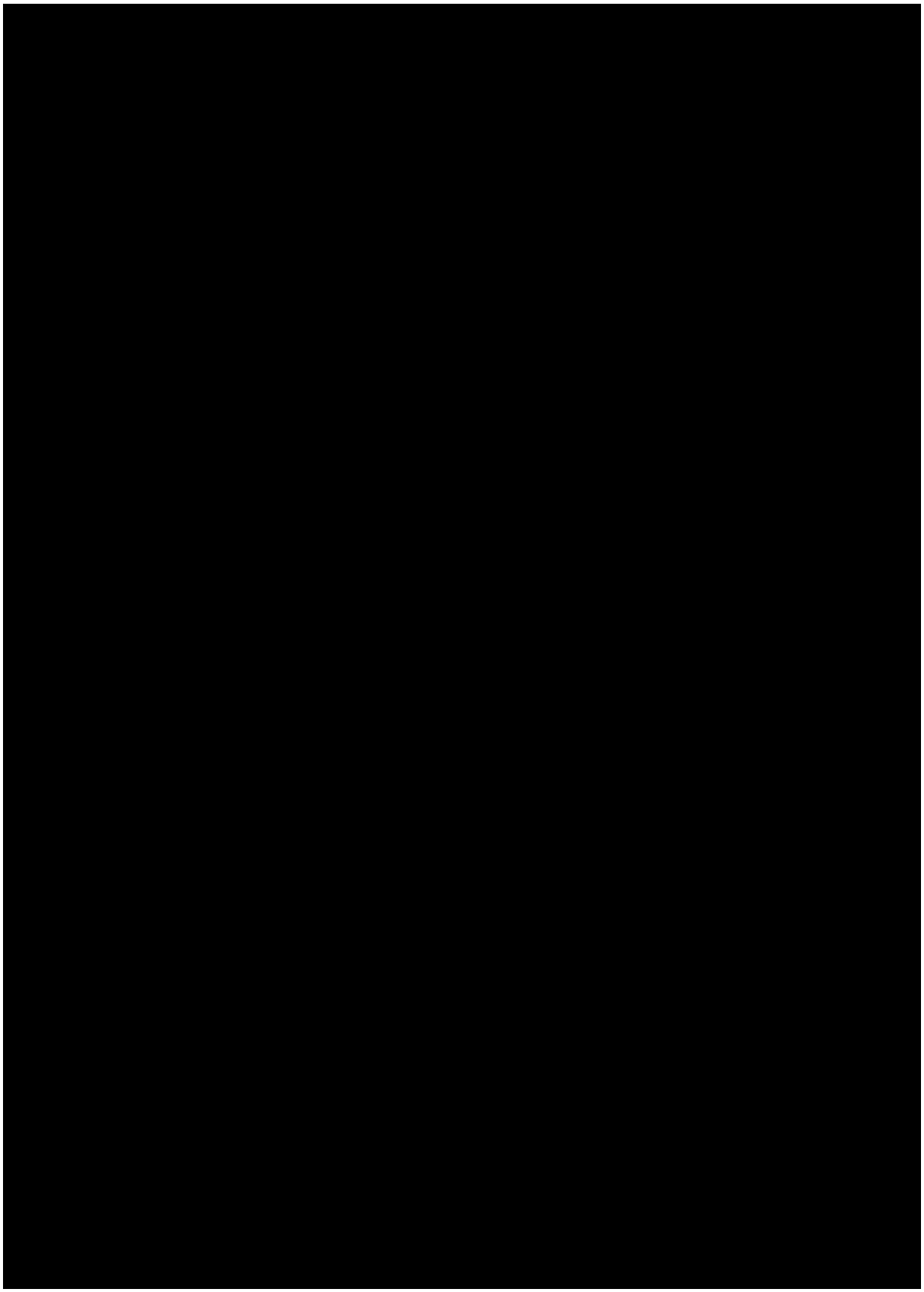
[4] NMPA. Guideline on General Considerations in Drug Clinical Trials. 18 January 2017.

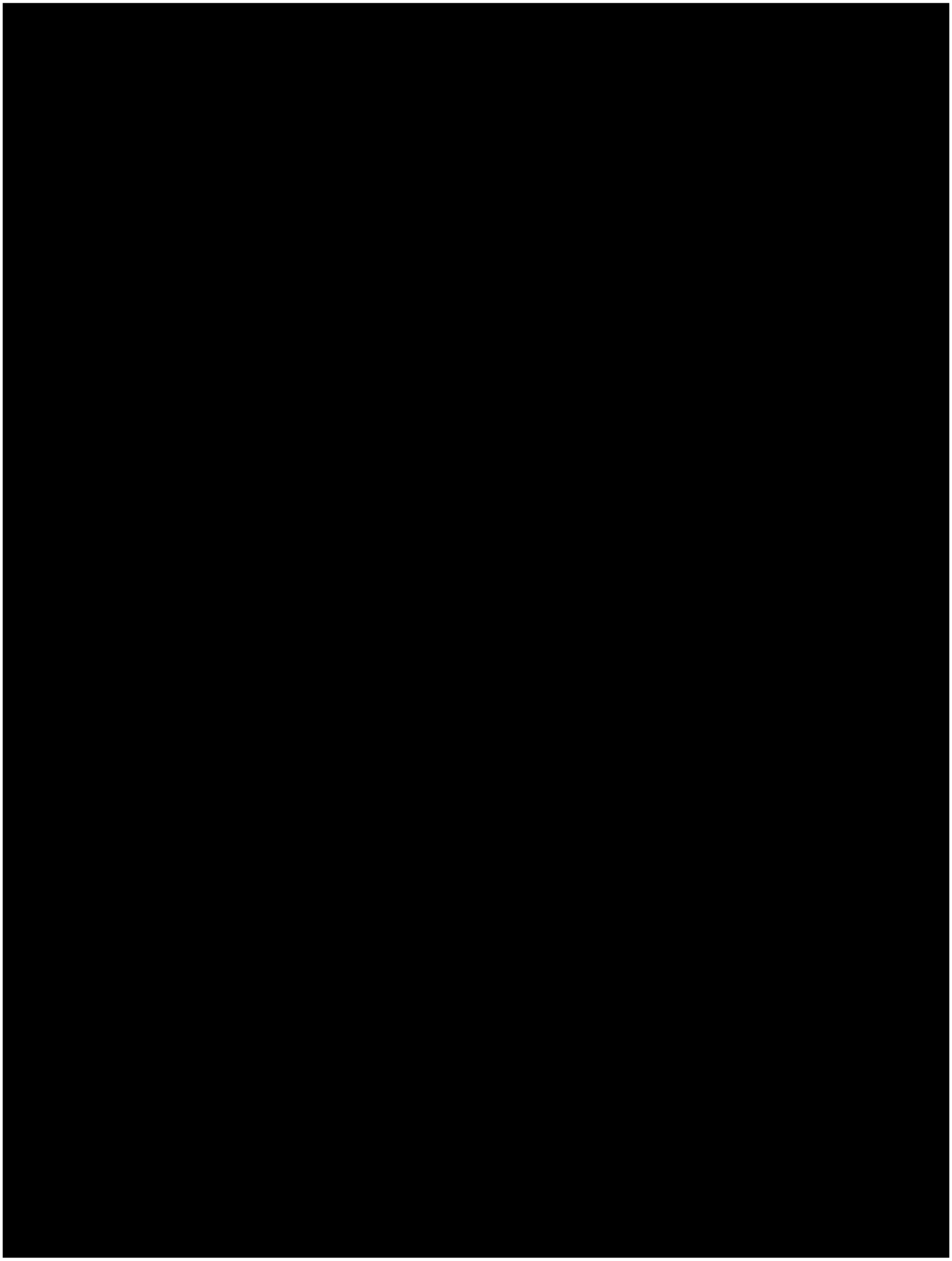
[5] Ingeborg M. B, Suzanne W, Charles E. A, et al. Revision of the ISN/RPS classification for lupus nephritis: clarification of definitions, and modified NIH activity and chronicity indices. Kidney Int. 2018; 93 (4): 789-796.

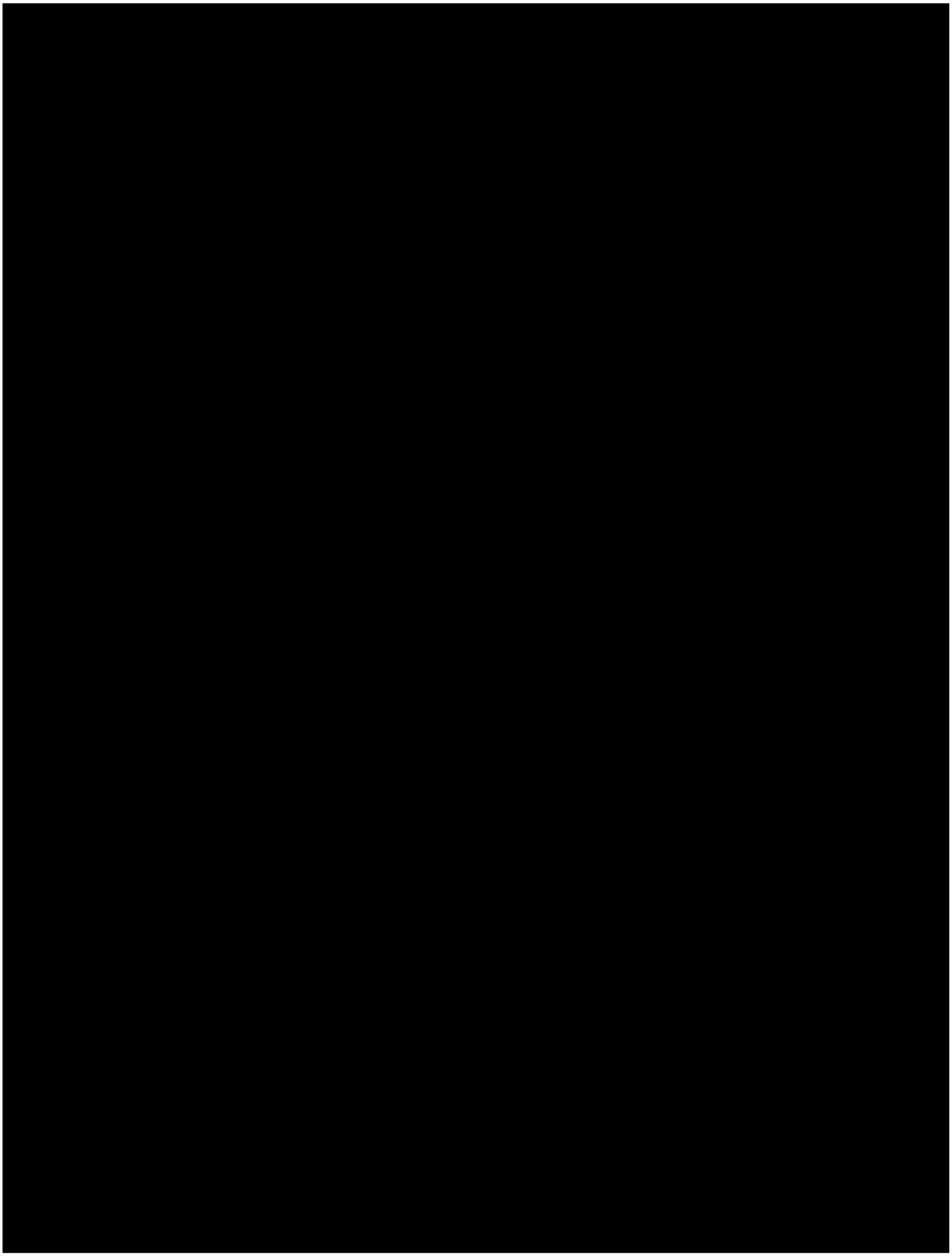
[6] Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int.2021; 100 (4S): S1-S276.

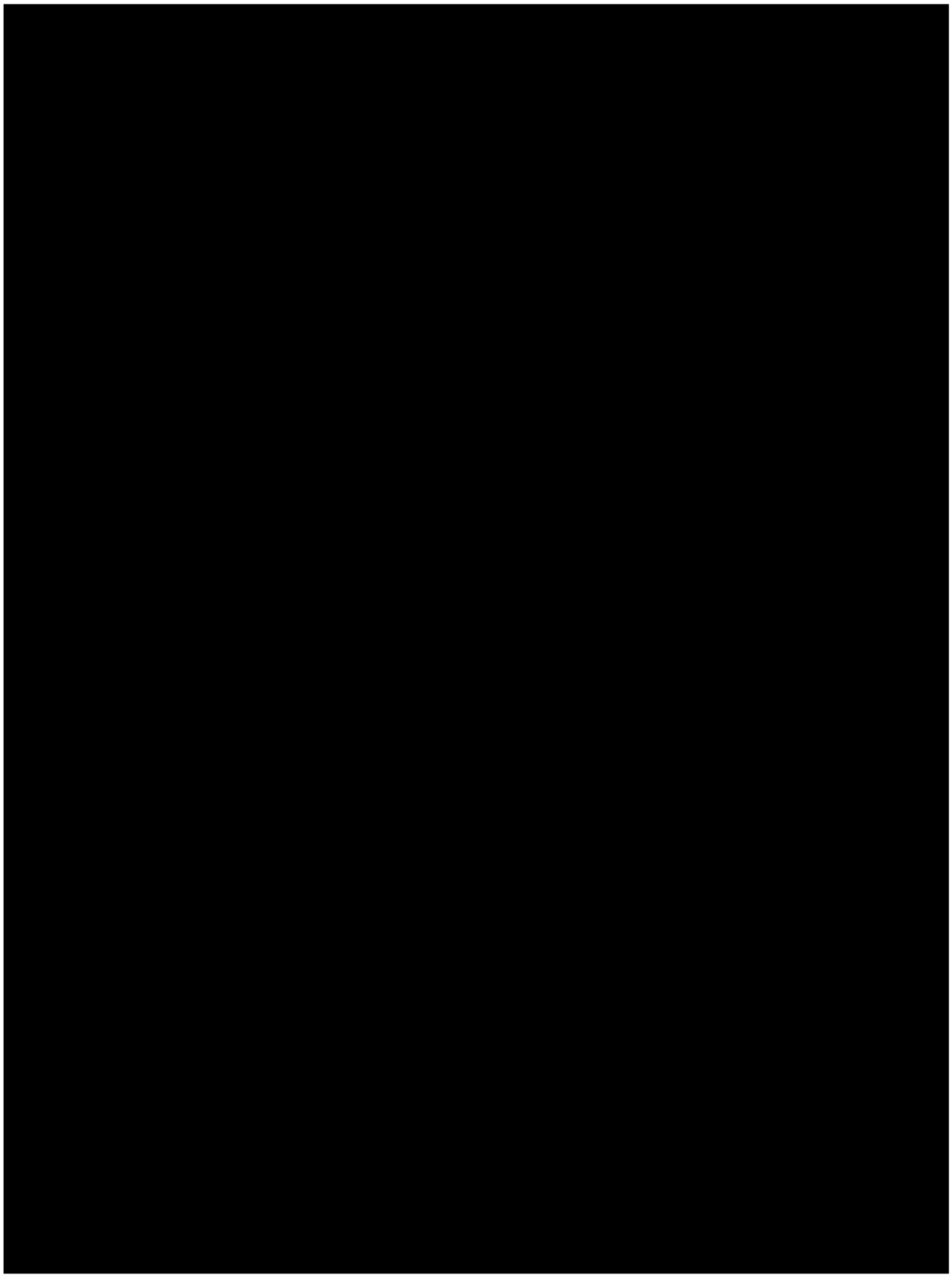
APPENDIX 5. GLUCOCORTICOID TOXICITY INDEX REQUIREMENTS DOCUMENT

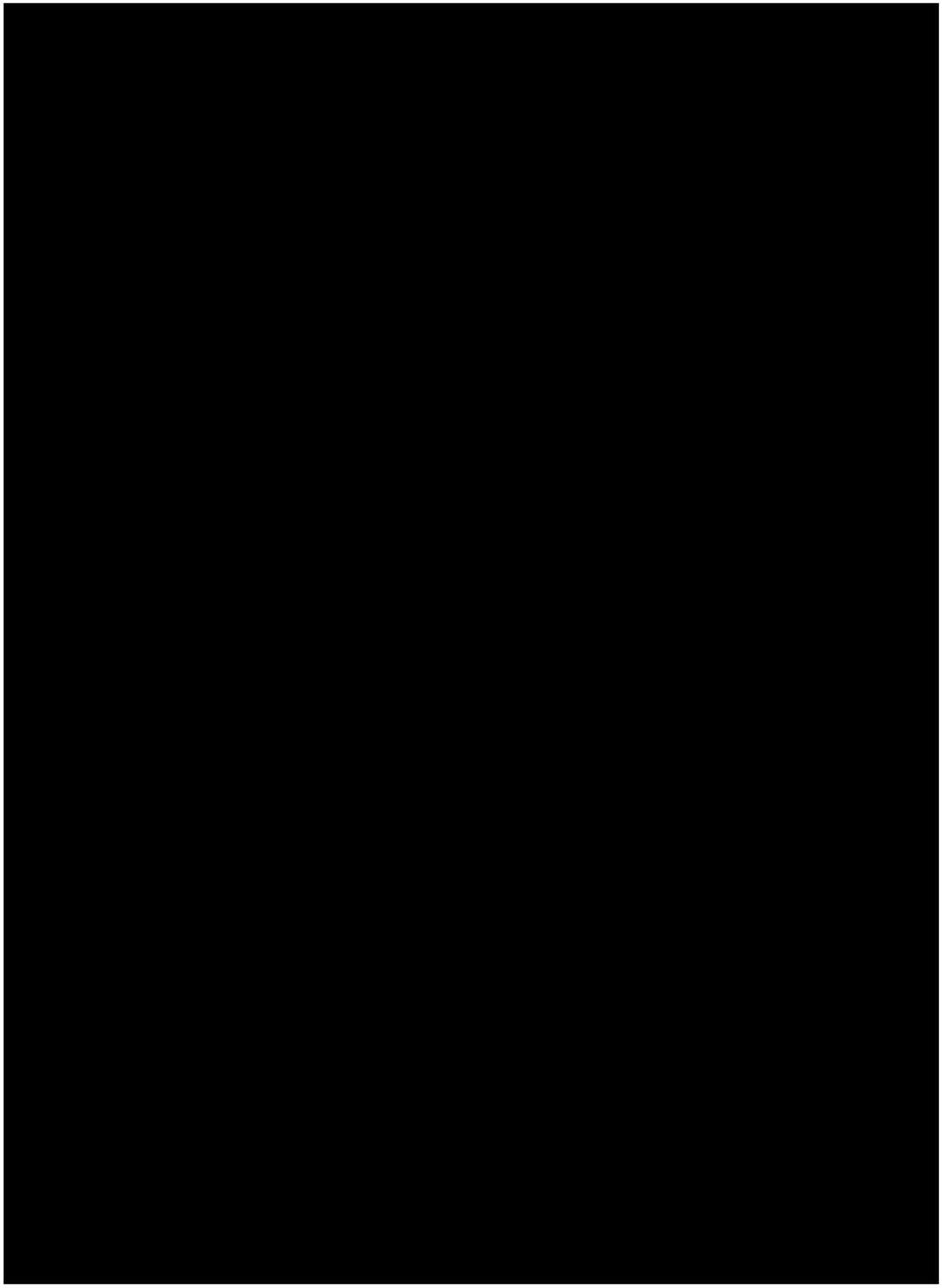


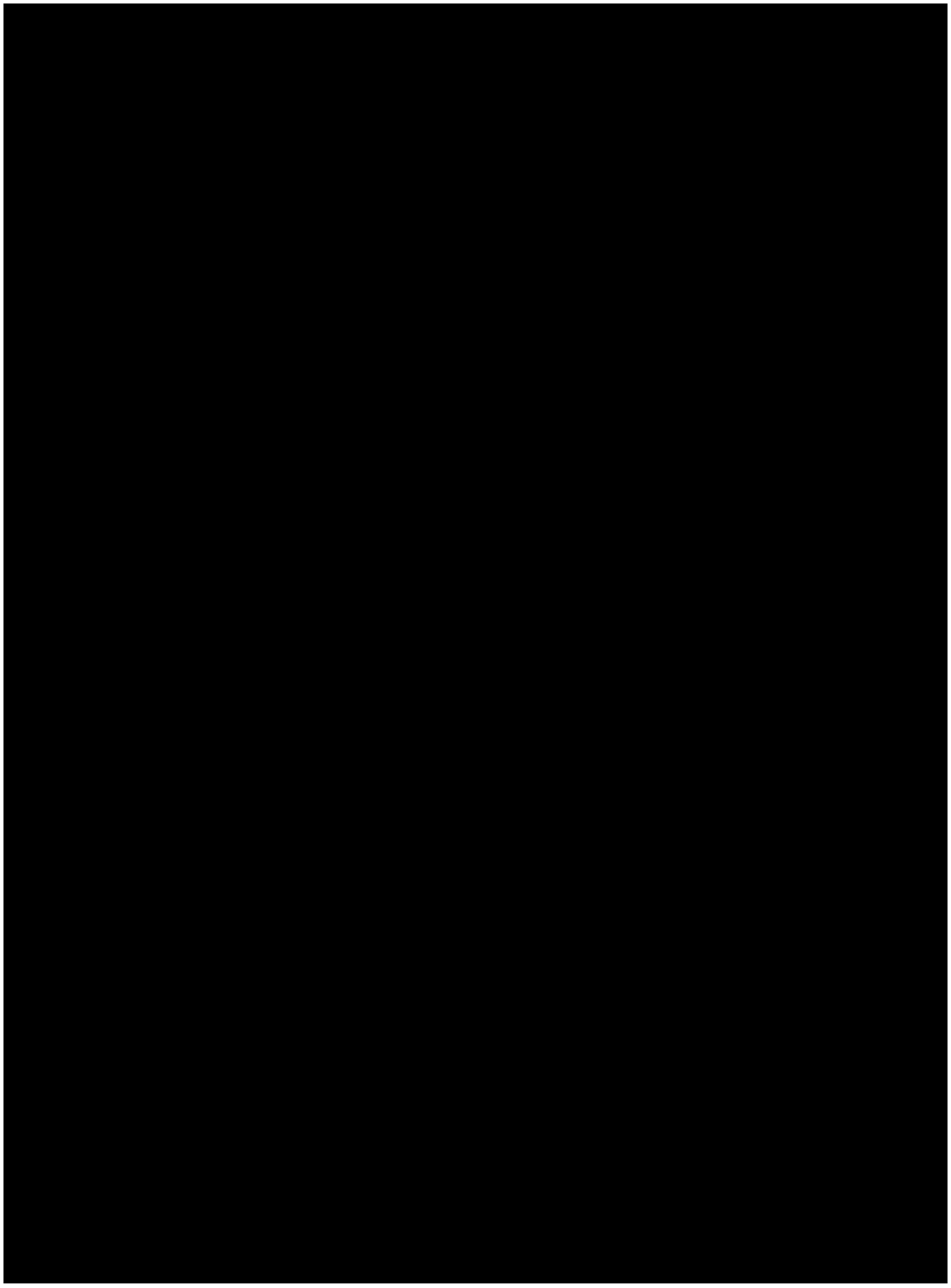


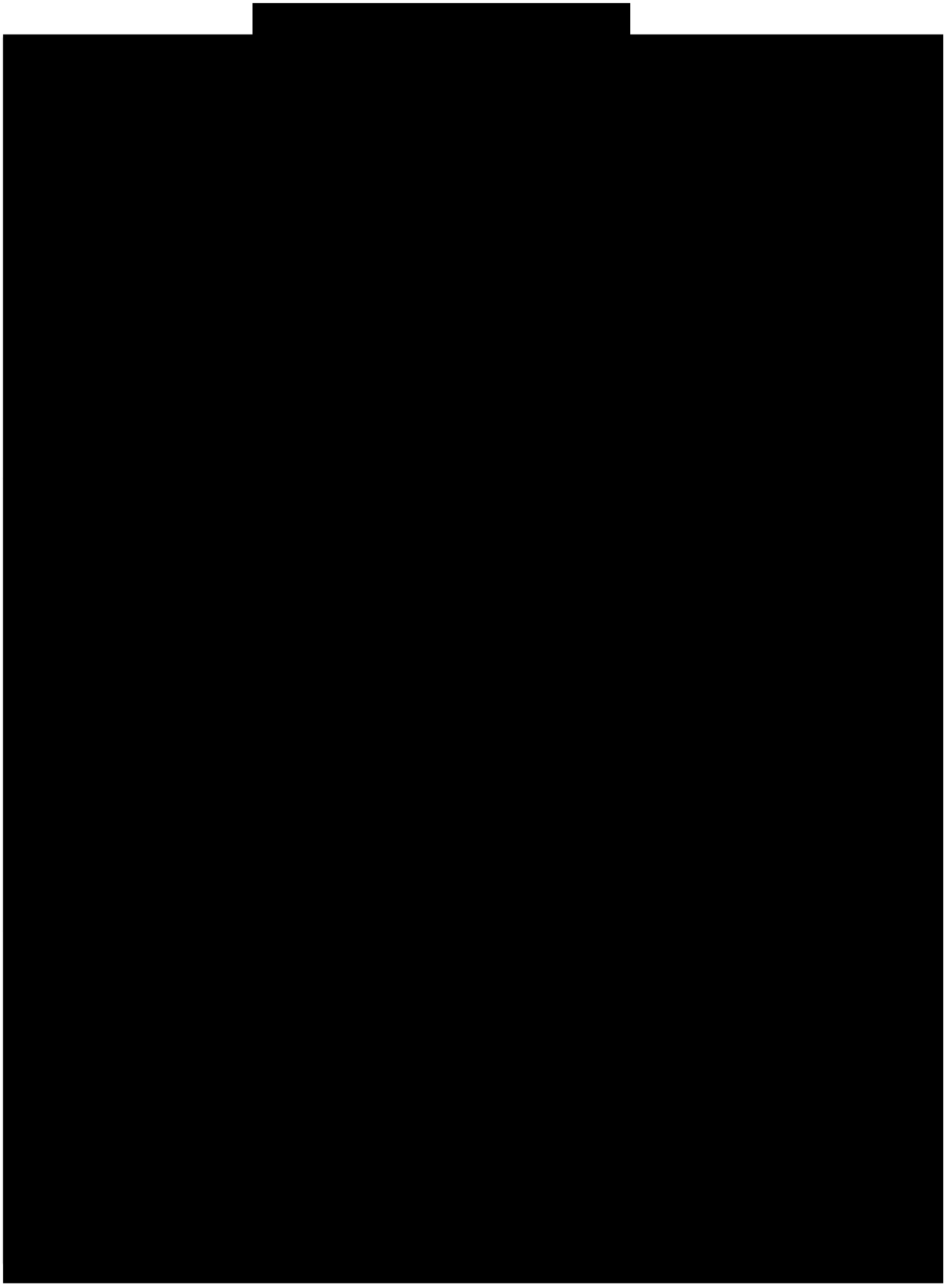


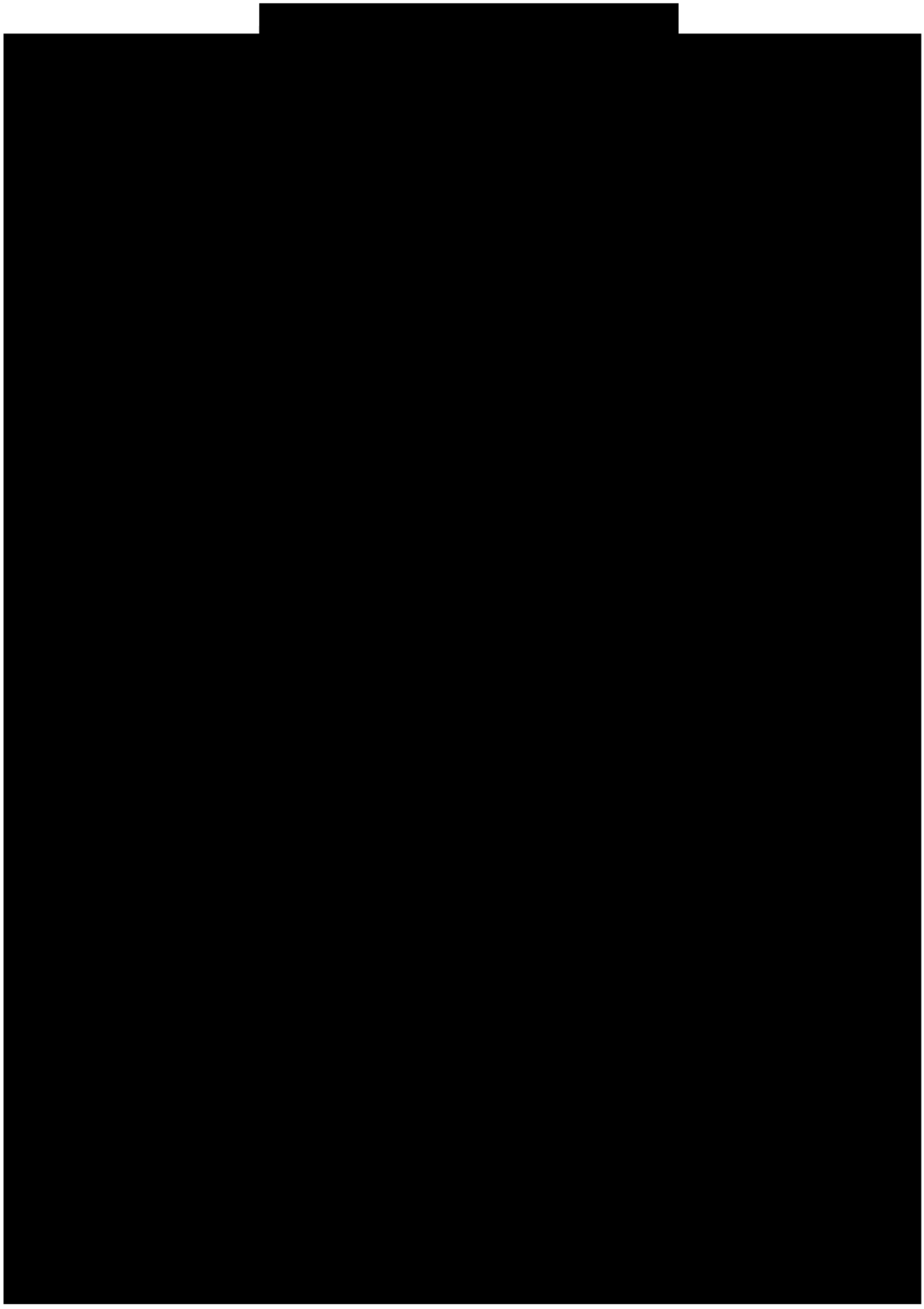


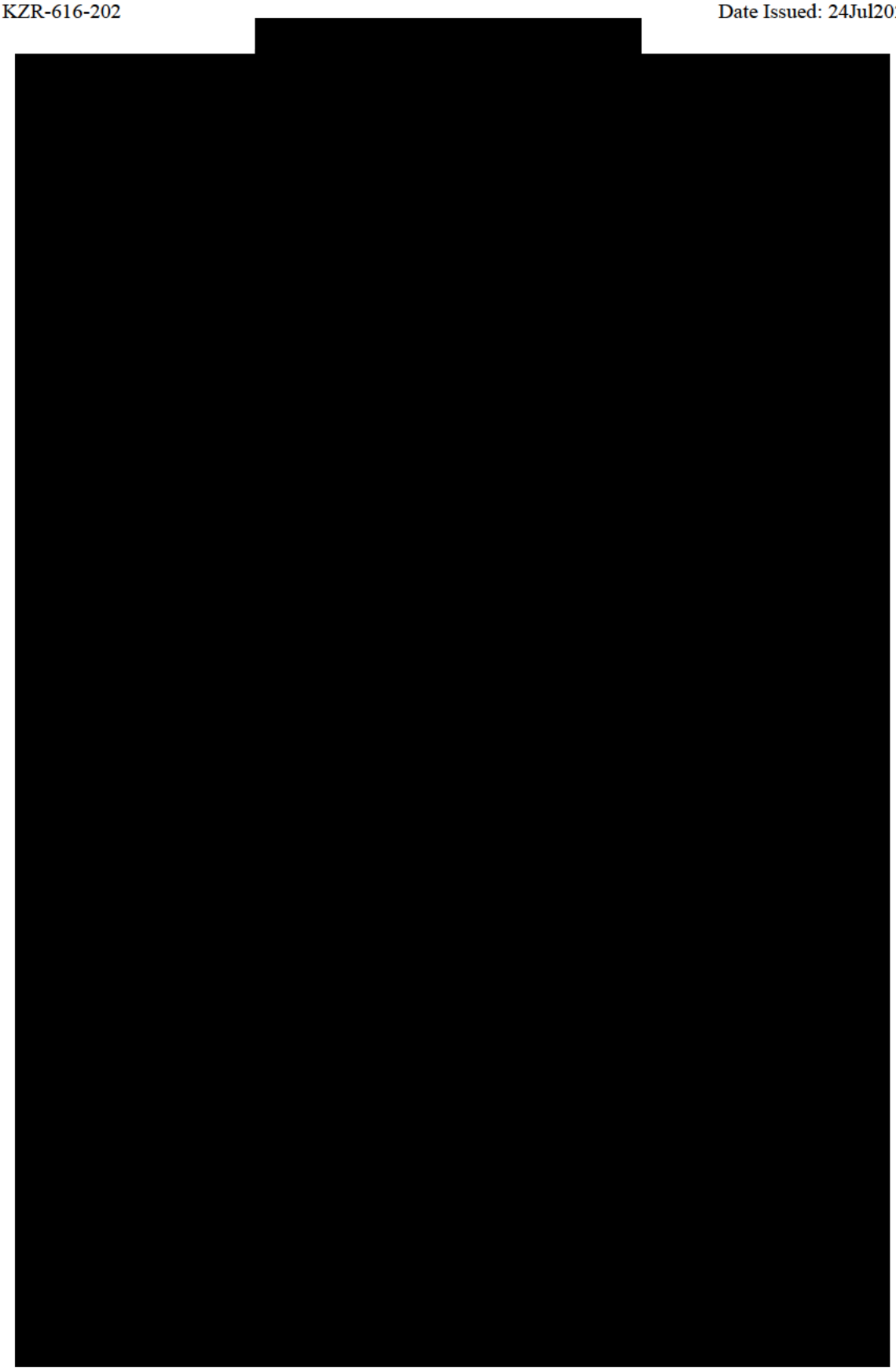


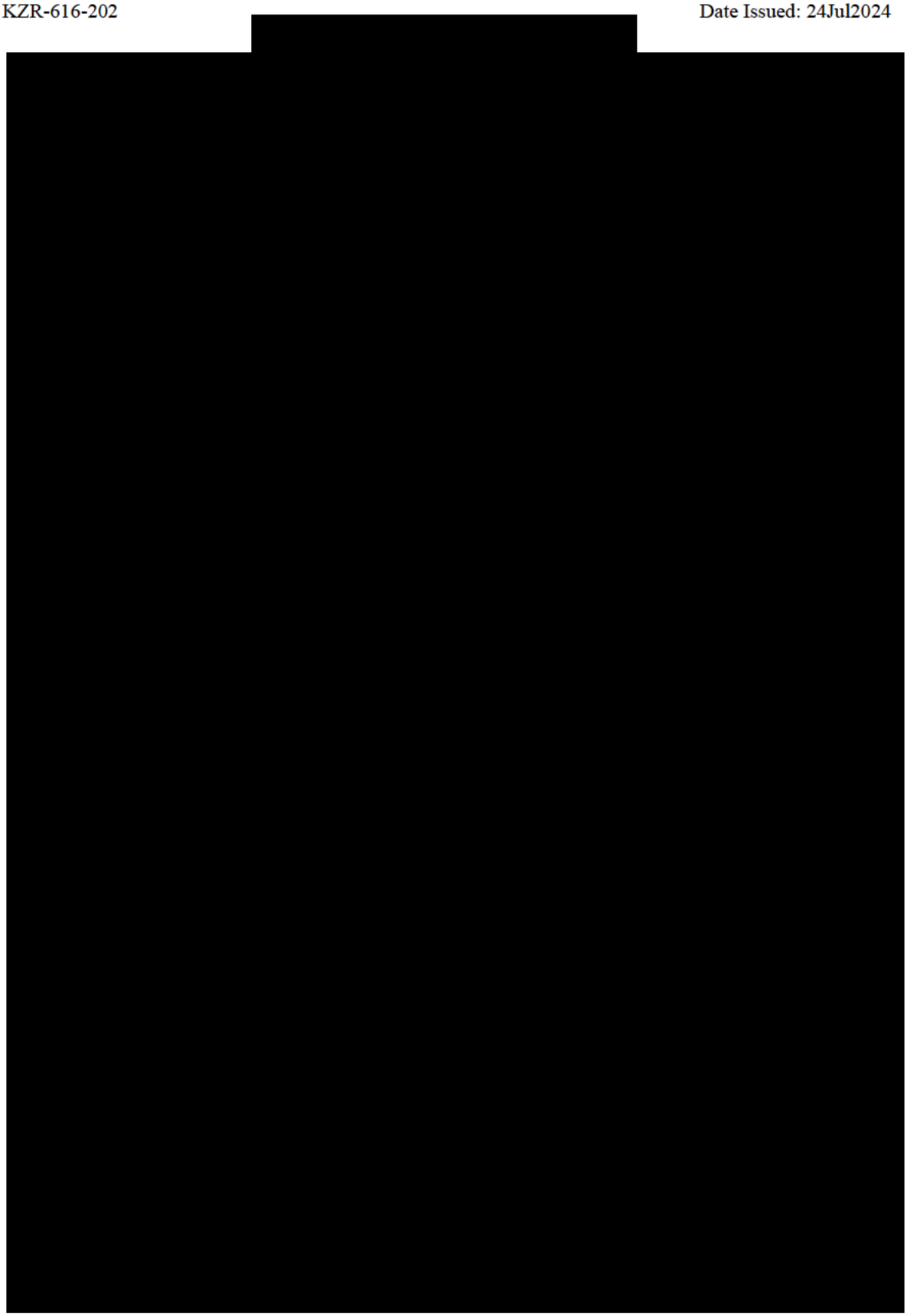


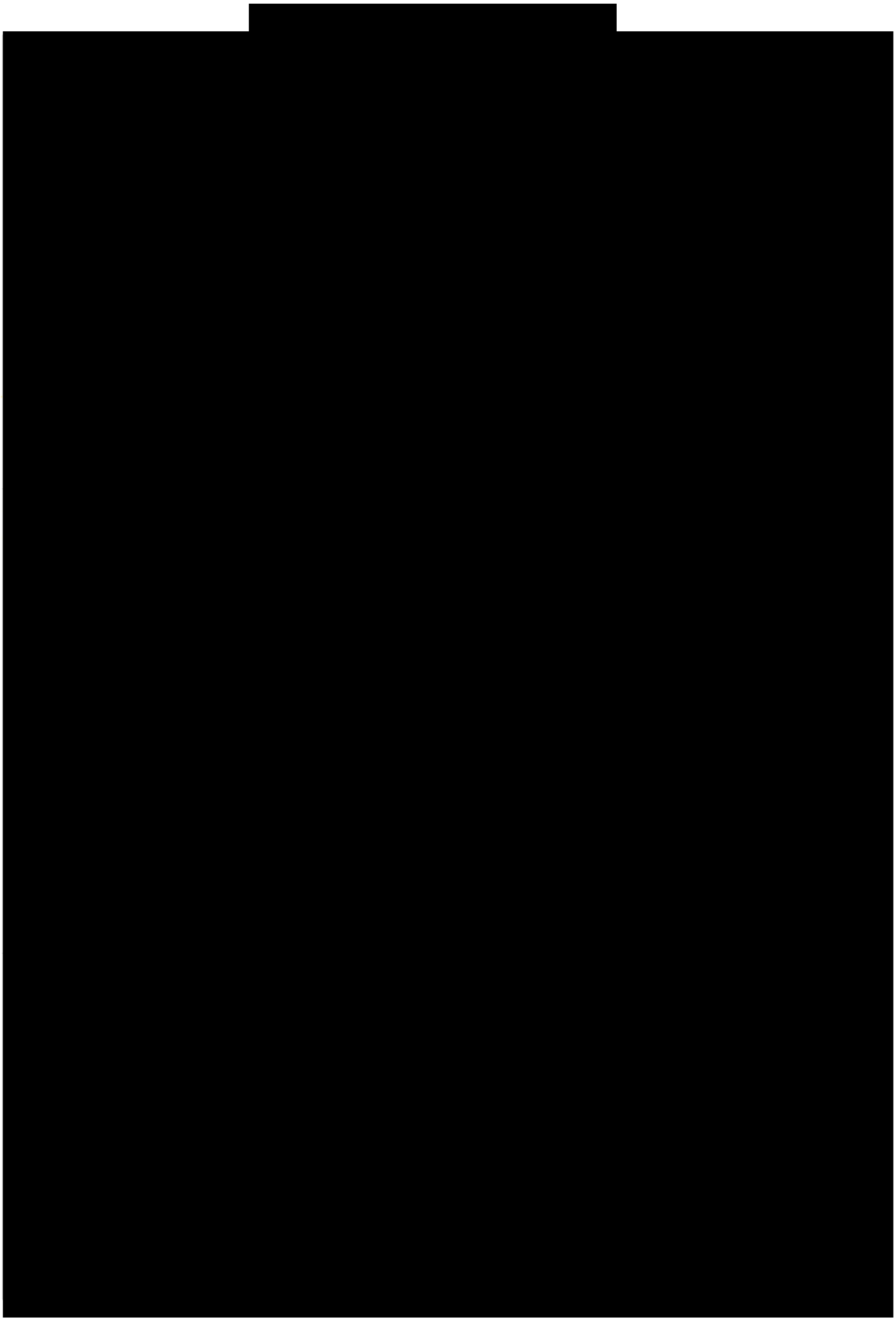












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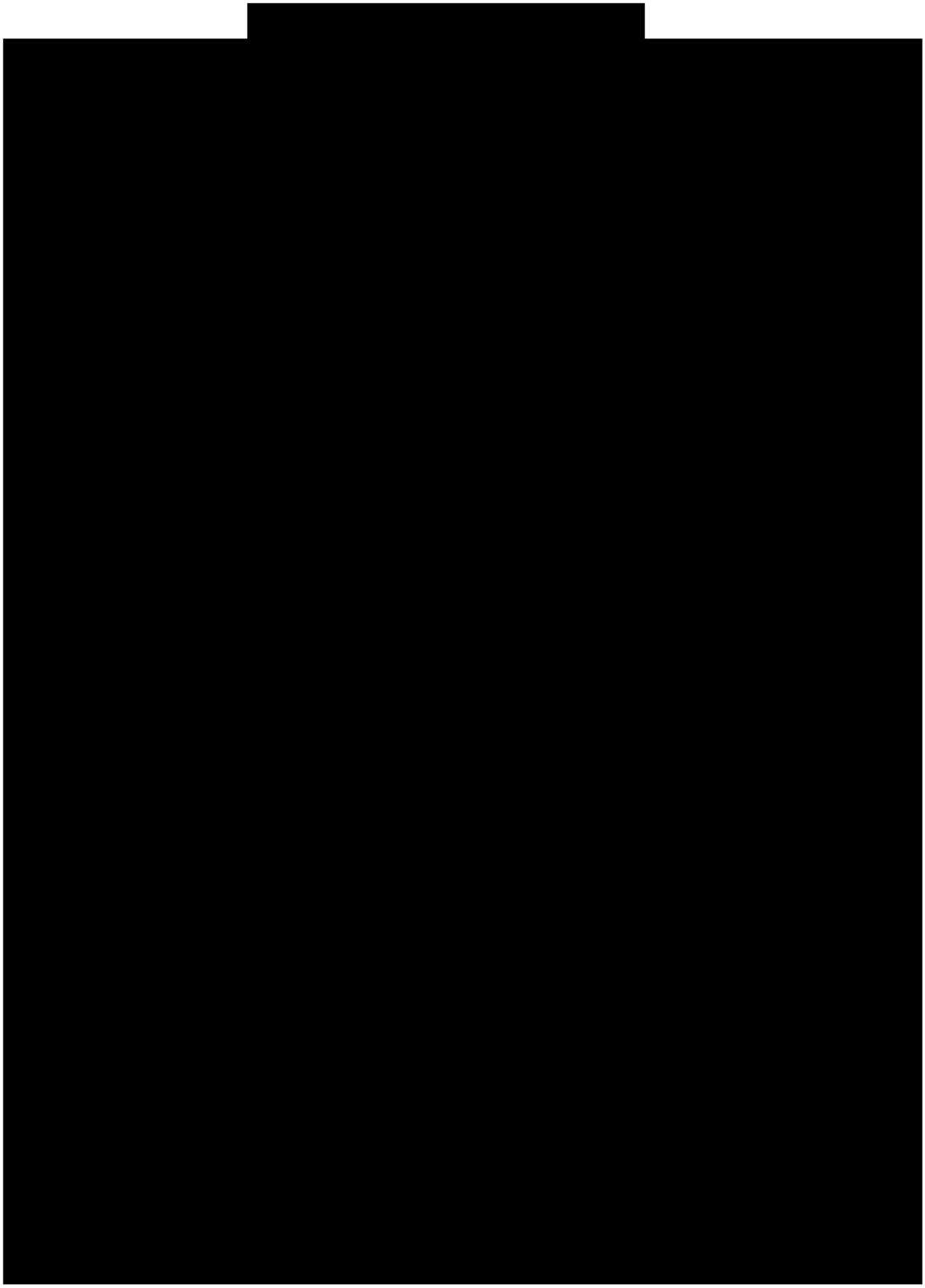
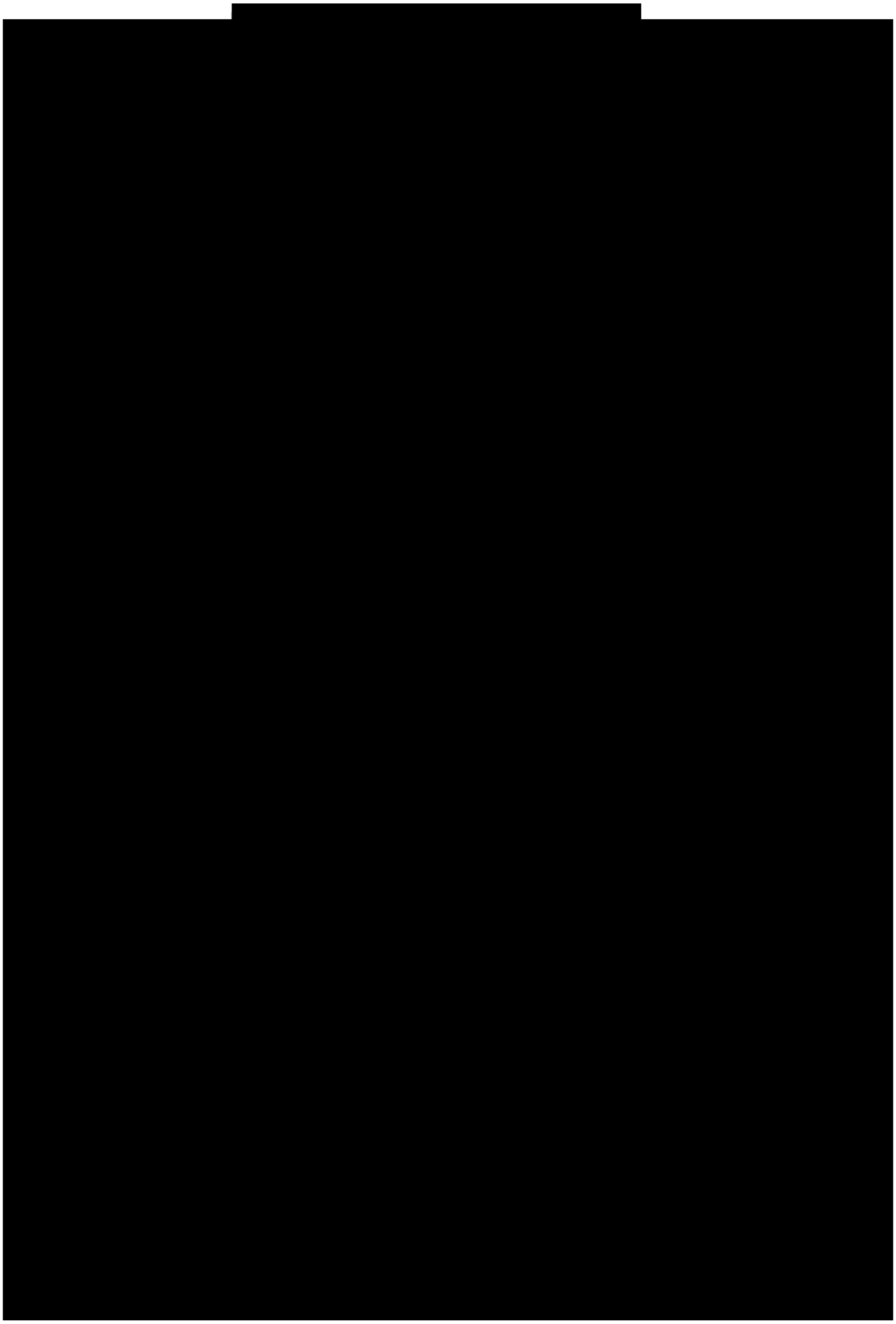


APPENDIX 6. WEIGHTING, SCORING, AND ANALYSIS OF THE GLUCOCORTICOID TOXICITY INDEX



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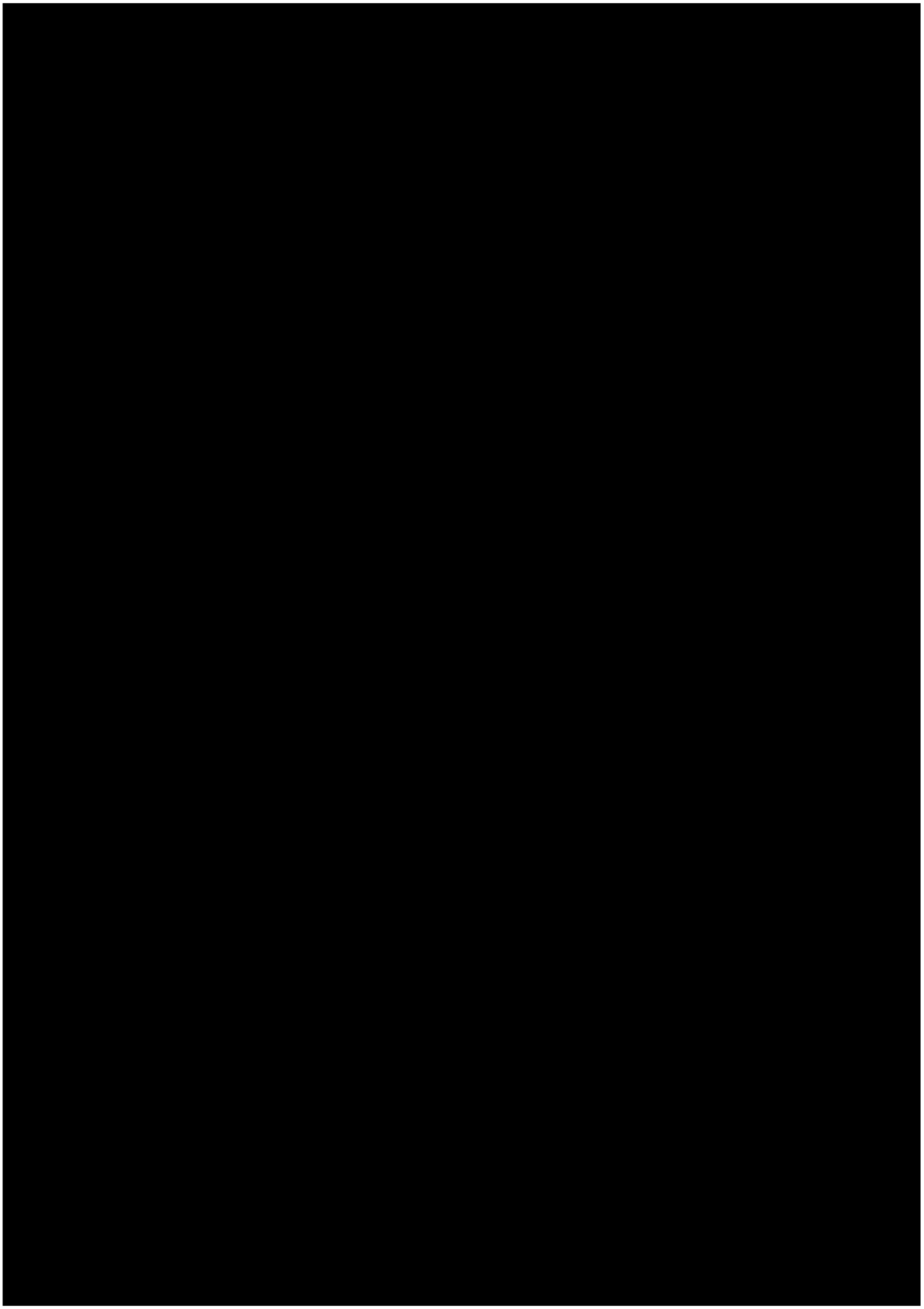
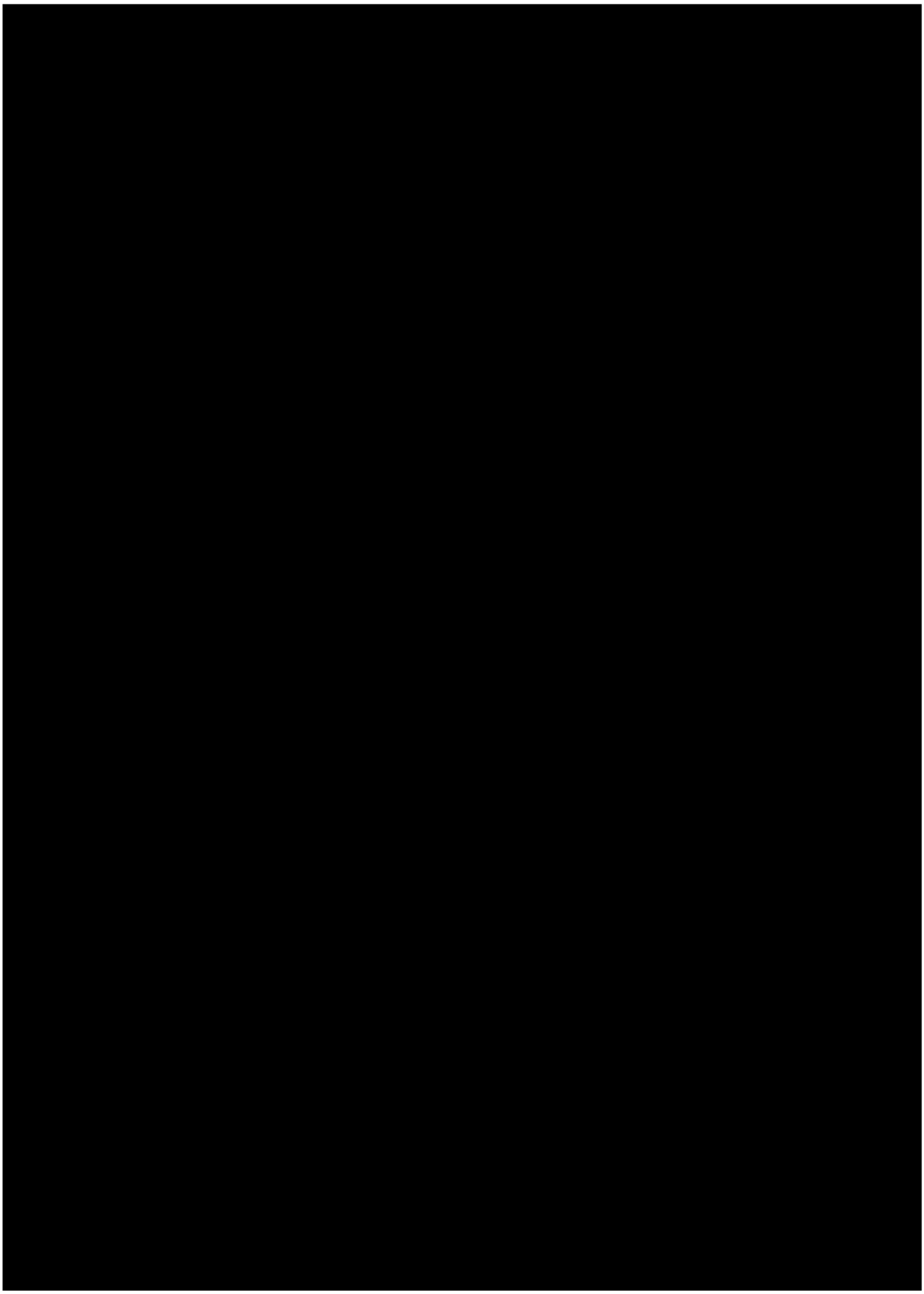
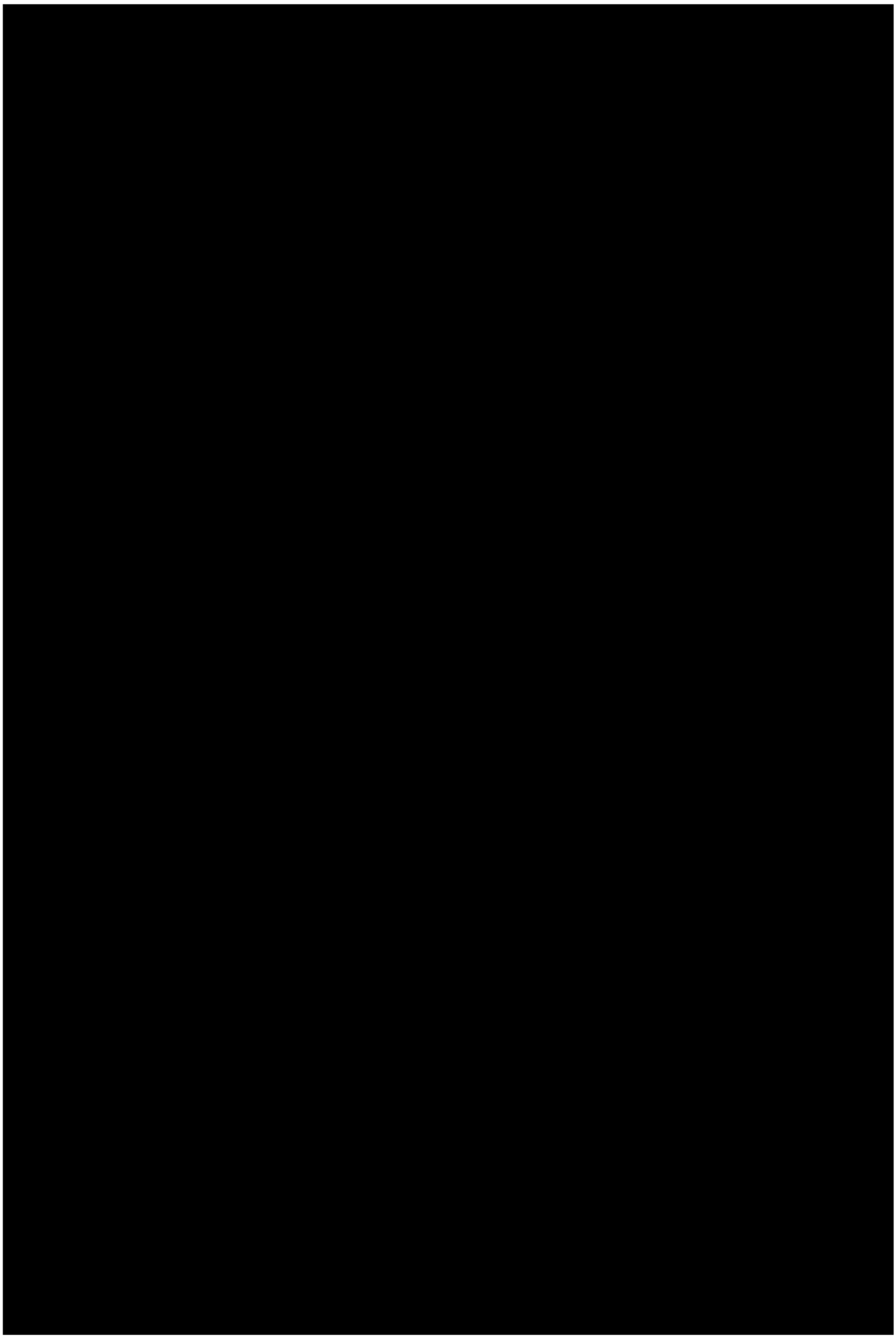
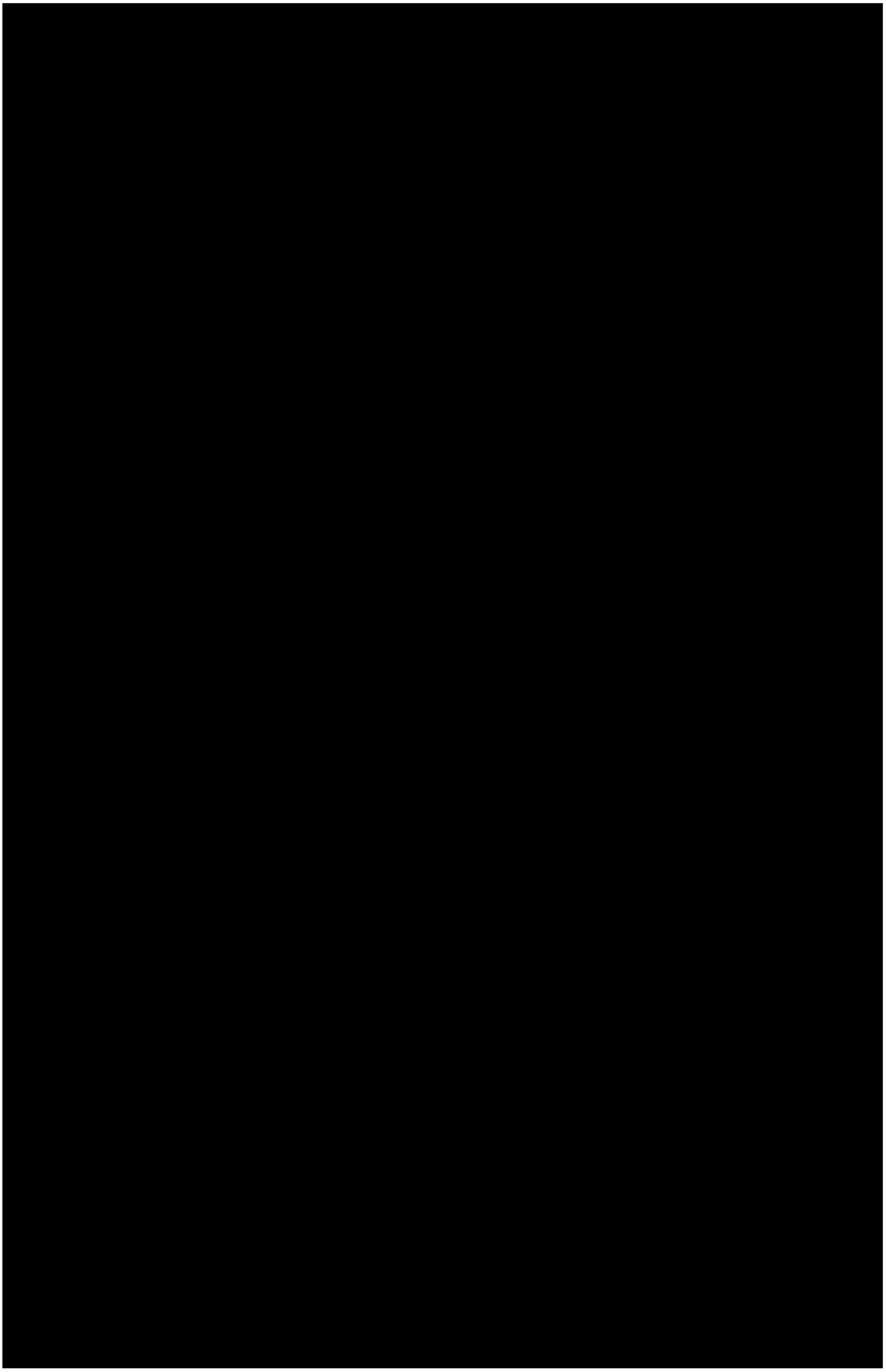








APPENDIX 7. SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX (SLEDAI-2K)

SLEDAI-2K (30 DAYS)

DATA COLLECTION SHEET

Study No.: _____ Patient Name: _____ Visit Date: _____ _____ _____
d m yr

(Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 30 days)

SLEDAI 2K Weight	SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.

4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.
TOTAL SCORE	_____		

Document Date: 10/2010

APPENDIX 8. SLE FLARE INDEX

SLEDAI FLARE INDEX

DATE:

☐☐ / ☐☐☐ / ☐☐☐☐

☐ Yes ☐ No Did the patient experience a Flare?

☐ Yes ☐ No Was there a Mild or Moderate Flare?

☐ Yes ☐ No Did the patient experience a Severe flare?

Experimental SELENA SLEDAI Flare Index

☐ Mild or ☐ Moderate Flare

☐ Change in SLEDAI instrument score of 3 points or more (but not to more than 12)

☐ New/Worse:

- Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus
- Nasopharyngeal ulcers
- Pleuritis
- Pericarditis
- Arthritis
- Fever (SLE)

☐ >=1.0 increase in PGA score, but not to more than 2.5

☐ Increase in prednisone, but not to >0.5 mg/kg/day

☐ Added NDAID or hydroxychloroquine for SLE activity

Severe Flare

☐ Change in SLEDAI instrument score to greater than 12

☐ New/worse:

- CNS-SLE
- Vasculitis
- Nephritis
- Myositis
- Plt < 60,000
- Hemolytic anemia: Hb <70g/L or decrease in Hb >30 g/L

Requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization

☐ Hospitalization for SLE Activity

☐ New cyclophosphamide, azathioprine, methotrexate for SLE activity

☐ Increase in prednisone to >0.5 mg/kg/day

☐ Increase in Physician's Global Assessment to >2.5

APPENDIX 9. 28-JOINT COUNT

28-Joint Count

Assessment date: ☐☐ / ☐☐☐ / ☐☐☐☐ Time: ☐☐ : ☐☐

Joint Position		Reason Not Evaluable
1. Shoulder Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
2. Elbow Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
3. Wrist Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
4. Metacarpophalangeal (MCP) I Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
5. Metacarpophalangeal (MCP) II Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
6. Metacarpophalangeal (MCP) III Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
7. Metacarpophalangeal (MCP) IV Left	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	
Right	☐ None ☐ Tender ☐ Swollen ☐ Not Evaluable	

28-Joint Count continued

☐ Yes ☐ No Are there any other joints (not listed above) that are significantly affected by SLE?

If yes, list joint, joint position, and provide description including if joint is tender and/or swollen.

Joint:

Description:

Joint:

Description:

☐ Yes ☐ No Based on clinical exam/impression and patient report for the last 4 weeks, is there loss of functional range of movement sufficient to interfere with instrumental activities of daily living (eg, household chores, preparing meals, working, etc.)?

☐ Yes ☐ No In the last 4 weeks is there significant impairment of BASIC activities of daily living from active inflammation?

Please select all activities affected:

☐ 1 - Fixed Unit: Grooming

☐ 2 - Fixed Unit: Dressing

☐ 3 - Fixed Unit: Ambulating

☐ 4 - Fixed Unit: Toileting

☐ 5 - Fixed Unit: Feeding oneself

Assessor's Initials ☐☐☐

Shoulder finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Shoulder finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Elbow finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Elbow finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Wrist finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty

Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Wrist finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 1 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 1 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 2 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection

Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 2 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 3 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 3 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 4 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP4 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 5 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

MCP 5 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 1 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 1 finding not evaluable: Right

Amputation

Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 2 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 2 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 3 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 3 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion

Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 4 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 4 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 5 finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Finger PIP 5 finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure

Knee finding not evaluable: Left

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

Knee finding not evaluable: Right

Amputation
Ankylosis
Arthroplasty
Damage
Fracture
Fusion
Infection
Injection
Injury
Other Condition
Other Procedure
Surgery
Synovectomy

APPENDIX 10. PHYSICIAN GLOBAL ASSESSMENT (PGA)

Physician Global Assessment

Date:

☐☐ / ☐☐☐ / ☐☐☐☐

Physician's Global Assessment (PGA) Visual Analog Scale with anchors

Baseline PGA converted value: Previous PGA converted value:

During the Visit: At the time of the visit, it is recommended that the investigator mark the scale initially, but do NOT tick "assessment is final".

Please mark the scale with a **VERTICAL** line to indicate your assessment.

0 **1** **2** **3**

This scale should be completed by a sponsor provided scale on paper.

None Mild Moderate Severe

Measurement PGA converted value:

After the Visit: After all lab results have been received and reviewed, please indicate your final assessment. If you need to move the line based on lab results, please tick the "CLEAR" button to clear the existing line and re-draw the line according to your final assessment. Every effort should be made to make the final assessment within 14 days of the visit.

☐ Yes ☐ No Have lab results been reviewed prior to PGA completion?

IMPORTANT: The "Assessment is final" box should not be ticked until **all lab results from the visit are reported by central labs and reviewed by the Investigator**. When the assessment is final, please check the below box. Checking the box will lock the assessment and editing will not be possible.

☐ Assessment is final.

Physician's Global Assessment (PGA) completion date:

Assessor's Initials ☐☐☐

APPENDIX 11. EUROQOL 5-DIMENSION 5-LEVEL (EQ-5D-5L)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

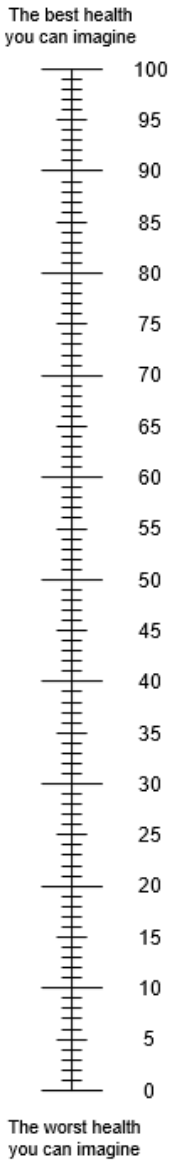
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 12. CLINICAL LABORATORY TESTS FOR SAFETY

Hematology	Serum chemistry (non-fasting)	Urinalysis	Coagulation and Other
hemoglobin	creatinine	pH	INR
hematocrit	creatine kinase	glucose	APTT
WBC count (total and differential)	urea (or BUN)	ketones	fibrinogen
neutrophil count	AST	blood	lupus anticoagulant panel
RBC count	ALT	protein	HbA1c
reticulocyte count	GGT	creatinine	Anti-dsDNA
platelet count	alkaline phosphatase	microscopy	Complement (C3 and C4)
MCV	LDH	leukocyte esterase	C1q autoantibody
MCH	total bilirubin	nitrite	Quantitative immunoglobulins (immunoglobulins M, G, and A)
MCHC	albumin	white blood cells	
	total protein	red blood cells	
	sodium	24-hour UPCR	
	bicarbonate	FMV UPCR	
	potassium	24-hour Proteinuria (Urine Protein 24 hr)	
	chloride		
	glucose		
	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; anti-dsDNA =anti double stranded deoxyribonucleic acid; FMV=first morning void; 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.

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Approval Task	[redacted] 26-Jul-2024 17:25:30 GMT+0000

Approval Task	[redacted] 26-Jul-2024 17:56:41 GMT+0000

Approval Task	[redacted] 26-Jul-2024 19:06:36 GMT+0000

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