TITLE PAGE

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF DAXDILIMAB IN ADULT PARTICIPANTS WITH ACTIVE PROLIFERATIVE LUPUS NEPHRITIS

PROTOCOL HZNP-DAX-203

Investigational New Drug (IND) Number: 127898

EudraCT Number: 2022-001377-31

VERSION 2.0

17 MAY 2022

Sponsor:	Horizon Therapeutics Ireland DAC 70 St. Stephen's Green Dublin 2, Ireland D02 E2X4
Sponsor Medical Expert:	[redacted], MD, MSc [redacted], Clinical Development Horizon Therapeutics 2400 Research Blvd Rockville, MD 20850 Telephone: 857-498-0977 [redacted]
Sponsor Signatory:	[redacted], PhD [redacted], Biostatistics, Biometrics Horizon Therapeutics 2400 Research Blvd Rockville, MD 20850 Telephone: 240-972-6134 [redacted]
Clinical Research Organization:	PPD Development, LP 929 North Front Street Wilmington, NC 28401

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PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
2.0 / 17 MAY 2022	Amendment 1	Clarification of eligibility criteria, removal of clinical evaluation instrument (GTI), update to clinical laboratory tests.
1.0 / 07 APR 2022	Initial version	N/A

N/A: not applicable

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable local regulations. The Principal Investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the institutional review board (IRB)/research ethics board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/REB before the changes are implemented to the study. All changes to the consent form will be IRB/REB approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this trial will be conducted according to this protocol, applicable local regulations, and ICH GCP guidelines.

Name	Title	Signature and date (DD-MMM-YYYY)
[redacted], MD, MSc	Senior Vice President, Clinical Development	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 18-May-2022 | 08:11 CDT FC5A89A7197943C6A4D17A0E5BCEFABB
[redacted], PhD	Sr. Director, Biostatistics, Biometrics	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 18-May-2022 | 08:14 CDT 94348E43E05145848D3DCFDE0A20F5C3

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(DD-MMM-YYYY)

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from Sponsor's representatives, ICH GCP guidelines, and applicable local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEI	Angiotensin-Converting Enzyme Inhibitor
ACR	American College of Rheumatology
[redacted]	[redacted]
ADA	anti-drug antibodies
ADR	adverse drug reactions
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANA	Antinuclear antibodies
anti-dsDNA	anti-double stranded deoxyribonucleic acid
anti-HBc	antibody to hepatitis B core antigen
APS	anti-phospholipid syndrome
ARB	Angiotensin II Receptor Blocker
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BCG	Bacille-Calmette-Guerin
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
Cl	clearance
CLASI-A	Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity
CLE	cutaneous lupus erythematosus
CONSORT	Consolidated Standards of Reporting Trials
C_{max}	maximum observed concentration
CMV	cytomegalovirus
COVID-19	Coronavirus Disease 2019
CRF	case report form
CRO	contract research organization
CRR	Complete Renal Response
CTCAE	Common Terminology for Adverse Events
DC	dendritic cell
DM	dermatomyositis
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ESRD	end-stage renal disease
ET	early termination

Abbreviation	Definition
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonization
IFN	interferon
Ig	immunoglobulin
IgG1λ	immunoglobulin G1 lambda
IGRA	IFN-gamma release assay
ILT7	immunoglobulin-like transcript 7
IND	Investigational New Drug
IP	investigational product
ITT	intention-to-treat
IRB	institutional review board
ISN	International Society of Nephrology
IV	intravenous
LLOQ	lower limit of quantification
LN	Lupus nephritis
LTE	long-term extension
LOCF	last observation carried forward approach
mAb	monoclonal antibody
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MMF	mycophenolate mofetil
MMRM	mixed models for repeated measures
MedDRA	Medical Dictionary for Regulatory Activities
MPA	mycophenolic acid
MPV	mean platelet volume
[redacted]	[redacted]
N/A	not applicable

Abbreviation	Definition
NIH	National Institutes of Health
NSAID	non-steroidal anti-inflammatory drugs
OCS	oral corticosteroids
ORR	Overall Renal Response
OTC	over-the-counter
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic
PLT	platelet
PM	polymyositis
PPD	purified protein derivative
PRR	Partial Renal Response
PT	Preferred Term
[redacted]	[redacted]
[redacted]	[redacted]
QC	quality control
RBC	red blood cell (count)
REB	research ethics board
RPS	Renal Pathology Society
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneously
SD	standard deviation
SDI	SLICC/ACR Damage Index
[redacted]	Safety of Estrogens in Lupus Erythematosus National Assessment
SFU	Safety follow-up
SGLT2	Sodium-Glucose Cotransport 2
SID	sample identification
SLE	systemic lupus erythematosus
SOC	Standard-of-care
[redacted]	[redacted]
$t_{1/2}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse events
TEAESIs	treatment-emergent AEs of special interest
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
VAS	Visual Analogue Scale
V_{ss}	volume of distribution at steady state

Abbreviation	Definition
WBC	white blood cell (count)
WHO	World Health Organization
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:	**Name of Investigational Product:**	**Name of Active Ingredient:**
Horizon Therapeutics Ireland DAC	Daxdilimab (HZN-7734)	Daxdilimab (HZN-7734)

Protocol Title:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Evaluating the Efficacy and Safety of Daxdilimab in Adult Participants with Active Proliferative Lupus Nephritis

Phase of Development:

Phase 2

Trial Center(s):

This multicenter trial will be conducted at approximately 105 trial centers internationally.

Target Population:

Adults aged ≥ 18 to ≤ 80 years who have documented active, proliferative lupus nephritis (LN).

Number of Participants (planned):

The trial is planned to enroll approximately 210 participants. Participants will be randomized to 3 treatment groups, with approximately 70 participants to each treatment group.

Duration of Trial:

The maximum trial duration per participant is approximately 116 weeks, as follows:

- Screening Period: approximately 4 weeks (Days -28 to -1)
- Treatment Period: 104 weeks
- Safety Follow-Up (SFU) Period: 8 weeks (12 weeks after the last study intervention administration at Week 100)

Investigational Product [IP], Dosage, and Mode of Administration:

[redacted]

Randomized participants will receive either daxdilimab [redacted] mg or [redacted] mg administered subcutaneously (SC) as [redacted]

At [redacted], all participants will be assigned to a [redacted] based upon the renal response observed at [redacted] All participants, regardless of treatment assignment, who are unable to achieve at least a [redacted] in addition to SOC therapy. Participants who achieve at least a [redacted] and were randomized to

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daxdilimab treatment with either [redacted] in addition to SOC therapy.

Further guidance and information for the packaging, labeling, preparation, and administration of the Investigational Product are provided in the Pharmacy Manual.

Reference therapy, dosage, and mode of administration:

Placebo will be procured as commercially available Normal Saline and will be administered SC to randomized participants at baseline, [redacted] in addition to SOC therapy.

At [redacted] participants who were originally assigned to treatment with placebo and achieved at least a [redacted] in addition to SOC therapy.

Further guidance and information for the packaging, labeling, preparation, and administration of the placebo are provided in the Pharmacy Manual.

Stratification:

Randomization will be stratified by:

- Pre-randomization urine protein to creatinine ratio (UPCR) < 3.0 mg/mg vs. ≥ 3.0 mg/mg
- Screening estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 vs. ≥ 60 mL/min/1.73m^2

Objectives and Endpoints:

Primary Objective and Endpoint

Primary Objective	Primary Endpoint
To evaluate the efficacy of daxdilimab in combination with SOC compared to placebo in combination with SOC in participants with active, proliferative LN.	Proportion of participants achieving CRR at [redacted] CRR is defined as meeting all of the following: • eGFR ≥ 60 mL/min/1.73m^2 or no worse than 15% below baseline • 24-hour UPCR ≤ 0.5 mg/mg • No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment

Secondary Objectives and Endpoints

Secondary Objectives	Secondary Endpoints

To assess ORR (defined as CRR plus PRR) with daxdilimab versus placebo in participants with active, proliferative LN.	Proportion of participants achieving ORR at [redacted] See above for definition of CRR. PRR is defined as meeting all of the following: • eGFR ≥ 60 mL/min/1.73m^2 or no worse than 15% below baseline • Improvement in 24-hour UPCR: – For participants with a baseline UPCR ≤ 3.0 mg/mg: < 1.0 mg/mg – For participants with a baseline UPCR > 3.0 mg/mg: > 50% improvement from baseline and ≤ 3.0 mg/mg • No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment
To assess the change from baseline in eGFR with daxdilimab versus placebo in participants with active, proliferative LN.	• Change from baseline in eGFR at Week 52.
To evaluate the ability to improve dose requirements of oral corticosteroids (OCS) with daxdilimab versus placebo in participants with active, proliferative LN.	Proportion of participants able to taper OCS to ≤ 2.5 mg/day prednisone-equivalent by Week 24 and maintain this dose through Week 52. Sustained reduction of OCS dose: • Prednisone-equivalent dose ≤ 2.5 mg/day by Week 24 and not exceeding this dose through Week 52, and • No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment
To characterize the pharmacokinetics (PK) and immunogenicity of daxdilimab in participants with active, proliferative LN.	• Serum concentration of daxdilimab. • Rate of anti-drug antibodies (ADA) directed against daxdilimab and ADA titer for the duration of the study.
To evaluate the safety and tolerability of daxdilimab in combination with SOC in participants with active, proliferative LN.	• Incidence of treatment-emergent adverse events (TEAEs). • Incidence of treatment-emergent serious adverse events (TESAEs). • Incidence of treatment-emergent AEs of special interest (TEAESIs): hypersensitivity reaction, including anaphylaxis, severe (Grade 3 or higher) viral infection/reactivation, herpes zoster, opportunistic infection, and malignancy (except non-melanoma skin cancer).
[redacted]	

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Adjudication Committees and Data Monitoring Committee:

Adjudication Committee	An external Renal Pathology Adjudication Committee will evaluate the qualifying renal biopsies post-randomization and post-treatment biopsies to confirm the validity of local readings for the major classes of LN (ie, III, IV, and V) and to provide uniform, high-quality readings of more detailed assessments of the biopsies to better understand the relationship between histological findings and renal response in the study.
Data Monitoring Committee	An external, independent Data Safety Monitoring Board (DSMB) will evaluate safety data at regular intervals throughout the study and make recommendations to the Sponsor as needed. [redacted] This futility analysis is designed to be non-binding, so the DSMB may elect not to recommend terminating the trial after considering all of the data, even if the pre-specified futility criteria is met.

Trial Design

This trial is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to assess the efficacy and safety of daxdilimab in patients with active, proliferative LN despite standard of care. An overview of the trial design is presented in the schematic provided in Section 1.2 and details of trial activities are provided in Section 1.3.

Approximately 210 participants will be randomized in a ratio of 1:1:1 (70 participants per group) to receive either daxdilimab SC or placebo SC in addition to SOC background therapy as described below:

Group	Treatment
1	[redacted]
2	
3	

At [redacted] participants from all three Treatment Groups (above) will be assigned to a [redacted] regimen based upon the renal response observed at [redacted] described below:

Group	Treatment
1	[redacted]

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[redacted]

Participants may enter the study taking daily OCS at a maximum dose of 0.5 mg/kg/day of prednisone-equivalent, not to exceed 40 mg/day, and must be on a stable dose for at least 10 days prior to Randomization. In addition, participants will receive IV methylprednisolone pulse 500 mg on the day of Randomization, prior to receiving the study intervention, unless they received a methylprednisolone pulse of ≥ 500 mg within 10 days prior to Randomization followed by a reducing taper of OCS for participants already taking OCS prior to entry. For participants who are not already taking prescribed mycophenolate mofetil (MMF) prior to Randomization, the dosing of MMF will start at 500 mg twice a day (BID) for a total daily dose of 1 gm/day for the first week, increasing to 1 gm BID for a total daily dose of 2 gm/day for the second and subsequent weeks (ie, beginning on Day 8). An equivalent dose of mycophenolic acid (MPA) may be used as an alternative to MMF.

The trial will comprise a Screening Period of approximately 4 weeks (Days -28 to -1), a Treatment Period with Randomization on Day 1 followed by treatment through [redacted] totaling 19 administrations for all Treatment Groups with assignment of a [redacted] maintenance regimen at [redacted] based upon the [redacted] and a SFU Period of 8 weeks (through Week 112). Under exceptional circumstances such as delayed laboratory results, drug washout, or the impact of Coronavirus Disease 2019 (COVID-19), the Screening Period may be increased by 2 weeks, upon approval by the Medical Monitor. In general, re-screening of participants may occur only in consultation with and approval by the Medical Monitor. The trial will be conducted on an outpatient basis. For all administrations, study intervention will be administered by site staff in the clinic and the participant will be observed for at least 60 minutes after the first three doses as well as at [redacted] Participants who prematurely [redacted] will be followed for regularly scheduled visits through [redacted] after the last study intervention administration, whichever is longer, unless participants withdraw consent of trial participation or are lost to follow-up. Participants should be followed to assess AE/SAEs for at least 12 weeks after the last study intervention administration, approximately 4, 8, and 12 weeks after the last study intervention dose, unless

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the participant withdraws consent. Participants who prematurely stop dosing after [redacted] but remain in the study will be complete the End-of-Treatment (EOT) Visit and the SFU Period, unless the participant withdraws consent. Participants will not automatically be removed from the trial if any administration of study intervention is missed.

Rescue therapy for worsening LN may be administered at the discretion of Investigators as clinically indicated. Rescue therapy includes the initiation of any new treatment for lupus or LN or an increase from baseline in the SOC background therapy (MMF/MPA or corticosteroids). For any rescue medications, study intervention may be continued after discussion with and approval by the Horizon Medical Monitor. However, if the participant receives a prohibited medication as a rescue, study intervention will be discontinued (See Section 6.7.2). Participants who receive rescue therapy will be considered treatment failures for subsequent endpoint analyses (such as CRR).

The primary assessment of the efficacy endpoints will be performed at [redacted]. The final evaluation of the double-blind Treatment Period will occur at [redacted]. The SFU Period will begin after completion of the [redacted] EOT Visit and will last for 8 weeks. All participants will continue to receive SOC immunosuppressive background therapy with MMF/MPA and OCS, unless the participant has successfully discontinued OCS. Participants will continue to follow all trial requirements and will return to the clinical site for the Week 112 End-of-Study Visit for final safety assessments, as described in the Schedule of Activities, and return all remaining trial-related supplies not previously returned.

Safety assessments, including monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, and monitoring of hematology and blood chemistry, will be performed.

Inclusion/Exclusion Criteria:

All participants must meet/provide all of the following criteria to be eligible for trial participation:

1. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] in the United States) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.
3. Adult men or women ≥ 18 and ≤ 80 years of age.
4. Fulfill the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for systemic lupus erythematosus (SLE) (Aringer et al, 2019).
5. Have at least one of the following at Screening per central lab:
    - Antinuclear antibodies (ANA) ≥ 1:80.
    - Anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies elevated to above normal range as established by the central laboratory (ie, positive results).
    - Anti-Smith antibodies elevated to above normal (ie, positive results).

6. Diagnosis of proliferative LN based on a renal biopsy obtained within 6 months prior to signing the informed consent form (ICF) or during the Screening Period:
    - Class III (± class V) or class IV (± class V) LN according to the World Health Organization (WHO) or 2003 ISN/RPS classification (based on local evaluation of renal biopsy).
    - Note: the local biopsy report will be used to confirm participant eligibility. The submission of the Screening biopsy sample (archived or fresh tissue block, slides, or digital pathology images) for adjudication is required to participate in the study.
7. Urine protein to creatinine ratio ≥1.5 mg/mg (113.17 mg/mmol), obtained via a 24-hour urine collection at both:
    - The start of Screening and
    - Within 14 days of expected date of Randomization. Without the results of the second sample, which will be used for stratification, participants cannot be randomized. The second sample may be collected after a minimum of 10 days after the Screening sample was obtained. The second sample may be repeated once, upon approval by the Medical Monitor (this will not be considered a re-screen). Typical turn-around time for results from central laboratory is up to 7 days. On rare occasion, an extension of the 28-day screening window is allowed if re-collection of the sample is necessary or the results needed for Randomization are delayed.
8. Estimated glomerular filtration rate (as calculated by the Modification of Diet in Renal Disease [MDRD] formula, with screening laboratory results for serum creatinine value) ≥ 35 mL/min/1.73 m^2.
9. Negative serum β human chorionic gonadotropin (β-hCG) test at Screening (females of childbearing potential only).

Note: if the result of the serum β-hCG test is borderline or thought to be false positive, the test may be repeated during the Screening Period. The participant may continue if the repeat test is negative.

- Women of childbearing potential (WOCBP)(including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have negative serum and urine pregnancy tests during Screening and Randomization, respectively.
- WOCBP who are sexually active with a non-sterilized male partner must agree to use a highly effective method of contraception (Table 1) from signing of the informed consent, and must agree to continue using such precautions through the end of the study follow-up or 6 months (approximately 5 half-lives) following the last dose of IP in the case of early withdrawal from the study, and refrain from egg retrieval/egg donation during this period. A decision about contraception after this point should be made by the participant and her regular healthcare providers.
- Sustained abstinence is an acceptable practice; however periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Table 1 Highly Effective Methods of Contraception

Physical Methods	**Hormonal Methods** [a]
Intrauterine device Intrauterine hormone-releasing system [b]	Combined (estrogen and progestogen-containing hormonal contraception) PO (combined pill)

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Bilateral tubal occlusion Vasectomized partner [c] Sexual abstinence [d]	Injectable Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [e] Injectable Implantable Intravaginal **NOTE**: because mycophenolate affects the metabolism of hormonal contraceptives and may reduce their effectiveness in women receiving MMF or MPA who are using hormonal contraceptives for birth control, the participant must employ an additional contraceptive method (eg, barrier method)

PO: oral(ly).

[a] Any change in hormonal birth control during the study requires use of at least two methods of highly effective contraception for at least two months.

[b] This is also considered to be a hormonal method.

[c] A vasectomized partner is a highly effective method of birth control provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] Sexual abstinence is considered to be a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant.

[e] Progestogen-only hormonal contraception where inhibition of ovulation is not the primary mode of action (minipill) is not accepted as a highly effective method.

10. Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the trial and continuing for at least 3 months (approximately 5 half-lives) after receipt of the last dose of daxdilimab and refrain from donating sperm during this period.

Exclusion Criteria:

Participants will be ineligible for trial participation if they meet **any** of the following criteria at the Screening and/or Day 1 Visits, as applicable:

General Exclusion Criteria

1. Individuals involved in the conduct of the study, their employees, or immediate family members of such individuals.
2. Any condition that, in the opinion of the Investigator or the Sponsor/Central Review Committee, would interfere with evaluation of the IP or interpretation of participant safety or study results.
3. Weight > 160 kg (352 pounds) at Screening.
4. History of allergy, hypersensitivity reaction, or anaphylaxis to any component of the IP or to a previous monoclonal antibody (mAb) or human immunoglobulin (Ig) therapy.
5. Known intolerance to ≤1.0 gm/day of MMF or equivalent dose of MPA.
6. Participation in another clinical study with an investigational drug within 4 weeks prior to Day 1 or within 5 published half-lives, whichever is longer.

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7. Breastfeeding or pregnant women or women who intend to become pregnant anytime from signing the ICF through 6 months after receiving the last dose of IP.
8. History of drug or alcohol abuse that, in the opinion of the Investigator, might affect participant safety or compliance with visits, or interfere with other study assessments.
9. Major surgery within 8 weeks prior to Screening or elective surgery planned from Screening through the end of the trial.
10. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to Screening through Randomization.
11. A diagnosis of pure Class V membranous LN based on a renal biopsy obtained within 6 months prior to signing ICF or during the Screening Period.
12. History of dialysis within 12 months prior to signing the ICF or expected need for renal replacement therapy (dialysis or renal transplant) within a 12-month period after enrollment.
13. History of, or current renal diseases (other than LN) that in the opinion of the Investigator could interfere with the LN assessment and confound the disease activity assessment (eg, diabetic nephropathy).
14. Known history of a primary immunodeficiency or an underlying condition such as known human immunodeficiency virus (HIV) infection, a positive result for HIV infection per central laboratory, splenectomy, or any underlying condition that in the opinion of the Investigator significantly predisposes the participant to infection.
15. During Screening, any of the following per central laboratory (tests may be repeated once within the same Screening Period to confirm results prior to Randomization):
    - Aspartate aminotransferase > 2.5× upper limit of normal (ULN)
    - Alanine aminotransferase > 2.5× ULN
    - Total bilirubin > 1.5× ULN (unless due to Gilbert's syndrome)
    - Serum IgG < 600 mg/dL (or < 6 g/L) or < 400 mg/dL (<4 g/L) if due to active SLE/LN
    - Neutrophil count < 1000/µL (or < 1.0×10^9/L) or < 500/µL (< 0.5×10^9/L) if due to active SLE
    - Platelet count < 50,000/µL (or < 50×10^9/L) or < 25,000/µL (< 25×10^9/L) if due to active SLE
    - Hemoglobin < 8 g/dL (or < 80 g/L) or < 7 g/dL (< 70 g/L) if due to active SLE
    - Glycosylated hemoglobin > 8% (or > 0.08)
    - Total lymphocyte count < 200 cells/mm^3
16. Confirmed positive test for hepatitis B serology defined as:
    - Hepatitis B surface antigen, or
    - Hepatitis B core antibody (HBcAb) and hepatitis B virus (HBV) DNA detected above the lower limit of quantitation (LLOQ) by reflex testing by the central laboratory at Screening.

Note that participants who are HBcAb positive at Screening will be tested every 3 months for HBV DNA. IP will be discontinued if the participant's HBV DNA levels are confirmed to exceed the LLOQ as per the central laboratory.

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17. Positive test for hepatitis C virus antibody unless documented as having had successful treatment of active hepatitis C infection.
18. Active tuberculosis (TB), or a positive IFN-gamma release assay (IGRA) test at Screening, unless documented history of appropriate treatment for active or latent TB. Note that participants with an indeterminate IGRA test result with well-documented previous treatment do not need to repeat testing and are eligible for randomization. Participants with an indeterminate IGRA test result can repeat the test, but if the repeat test is also indeterminate, they are excluded.
19. Any severe herpes virus family infection (including Epstein-Barr virus, cytomegalovirus [CMV]) at any time prior to Randomization, including, but not limited to, disseminated herpes, herpes encephalitis, recent recurrent herpes zoster (defined as 2 episodes within the last 2 years), or ophthalmic herpes.
20. Any herpes zoster, CMV, or Epstein-Barr virus infection that was not completely resolved 12 weeks prior to Randomization.
21. Any of the following within 30 days prior to signing the ICF and through Randomization:
    - Clinically significant active infection in the opinion of the Investigator, including ongoing, and chronic infection requiring antibiotics or antiviral medication (chronic nail infections are allowed).
    - Any infection requiring hospitalization or treatment with intravenous anti-infectives.
    - A participant with a documented positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test may be rescreened:
        - At least 2 weeks after a positive test if the participant is asymptomatic (no negative test result is required) OR
        - At least 3 weeks after symptomatic COVID-19 illness (no negative test result is required).
22. Opportunistic infection requiring hospitalization or parenteral antimicrobial treatment within 2 years prior to Randomization.
23. Any acute illness or evidence of clinically significant active infection on Day 1.
24. Clinically significant cardiac disease including unstable angina, myocardial infarction, congestive heart failure within 6 months prior to Randomization. Any cardiac condition including, but not limited to the following, if in the opinion of the Investigator or Medical Monitor, would increase the risk of study participation:
    - Inadequately controlled arrythmia
    - Uncontrolled hypertension
    - Presence of clinically significant abnormality on electrocardiogram (ECG)
25. History of cancer within the past 5 years, except as follows:
    - In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to Screening, or
    - Cutaneous basal cell or squamous cell carcinoma treated with curative therapy.
26. Receipt of a live vaccine within 4 weeks prior to Day 1.
27. Participant should be assessed for epidemiologic risk of COVID-19 (ie, recent exposure, high-risk housing) and for health-related risk of COVID-19 severity based on current understanding of risk factors for severe disease when making a decision regarding the individual's risk of participation.

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Participants who have COVID-19 or other significant infection, or in the judgment of the Investigator, may be at a high risk of COVID-19 or its complications, should not be randomized.

Disease-Related Criteria

28. Active severe or unstable neuropsychiatric SLE including, but not limited to: aseptic meningitis, cerebral vasculitis, myelopathy, demyelination syndromes (ascending, transverse, acute inflammatory demyelinating polyradiculopathy), acute confusional state, impaired level of consciousness, psychosis, acute stroke or stroke syndrome, cranial neuropathy, status epilepticus, cerebellar ataxia, and mononeuritis multiplex:
    a) That might cause the participant to be unable to fully understand the ICF

    OR

    b) In the opinion of the Investigator, protocol-specified SOC is insufficient to control neurologic features of SLE and utilization of a more aggressive therapeutic approach, such as adding IV cyclophosphamide and/or high dose IV pulse corticosteroid therapy or other treatments not permitted in the protocol, is indicated or anticipated.
29. Documented history of systemic sclerosis or diagnosis of SLE with overlapping systemic sclerosis.
30. History of, or current diagnosis of, catastrophic anti-phospholipid syndrome (APS) or APS-related thromboembolic event or pregnancy loss within 1 year prior to signing the ICF. Participants with APS adequately controlled by anticoagulants or aspirin for at least 12 weeks may be recruited to the study.
31. History of any non-SLE disease that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to signing the ICF.

Prior and Concomitant Therapy Criteria

32. Receipt of any of the following treatments within the following timeframes.
    - 6 weeks prior to Randomization:
        - Opioid use above 40 mg/day morphine-equivalent, unstable dosing, or initiation of regular dosing
        - IV corticosteroids > 3.0 gm (cumulative dose)
    - 8 weeks prior to Randomization:
        - Immunoglobulins (except anti-SARS-CoV-2 therapeutic antibodies)
        - Calcineurin inhibitors (eg, cyclosporin, voclosporin, tacrolimus), mechanistic target of rapamycin inhibitors, retinoids, thalidomide, lenalidomide, or Janus kinase inhibitors
        - Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis, plasma exchange, or Therakos® photopheresis
    - 12 weeks (or 5 half-lives, whichever is longer) prior to Randomization:
        - IV cyclophosphamide >2 pulses of high dose ($\geq$ 0.5 gm/m^2) or > 4 doses of low dose (500 mg every 2 weeks)
        - Alkylating agents other than cyclophosphamide (eg, chlorambucil)

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- Cytokine or cytokine receptor antagonists, including but not limited to interleukin (IL)-1, IL-6, IL 17, IL-12/23, IL-23, IFN, integrin, or TNFα antagonists (except for IFN-α kinoid, for which receipt at any time is exclusionary)
- Belimumab, abatacept, or eculizumab
- Other biologics used for immunosuppression or immunomodulation (eg, IFN therapy, IL-2)
- Investigational drugs
- IPP-201101 (Lupuzor™)

- 24 weeks prior to Randomization:
  - B cell-depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, inebilizumab, telitacicept) other than atacicept or obinutuzumab
  - Receipt of systemic glucocorticoids (ie, PO, rectal, IV or IM) for more than a total of 2 weeks for any concurrent illness, including asthma, inflammatory bowel disease, or drug-induced SLE
- 40 weeks prior to Randomization:
  - Atacicept
- 1 year prior to Randomization:
  - Bacille-Calmette-Guerin (BCG) vaccination
- 1.5 years prior to Randomization:
  - Obinutuzumab
- The following medications must be discontinued prior to the day of Randomization (because of potential interaction with MMF):
  - Methotrexate
  - Azathioprine
  - Leflunomide
  - Mizoribine
  - Proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole, etc.)
  - Cholestyramine

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Dosage Form and Strength of Formulation, Dosing and Administration:

[redacted]

Placebo is to be procured by the study sites as commercially available Normal Saline.

Study treatment (daxdilimab and placebo) is to be administered SC. To maintain the same number and volume of injections across all groups, the required dose will be administered by two 1.5 mL injections.

The first day of dosing is considered Day 1. To reduce the risk of unblinding to the study personnel who will be evaluating the participant, study intervention will be administered by an unblinded pharmacist/IP Manager or a study site staff member who is not otherwise involved in the participant's participation in the study. The study intervention administrator should be experienced in performing SC injections. The skin surface of the anterolateral thigh, upper outer triceps area, upper buttocks, or abdomen (avoiding a 2-inch [5 cm] radius around the umbilicus) should be prepared with an alcohol wipe and allowed to air dry. The skin will be pinched to isolate SC tissue from the muscle. The needle will be inserted at a 90-degree angle to the skin surface approximately halfway into the SC tissue. The prepared study intervention will be slowly injected (at least a 5 second duration is recommended per 1.5 mL syringe) into the SC tissue using gentle pressure. The area should not be massaged after injection. The SC injection site may be changed during the study as per the participant's preference.

Further guidance and information for the preparation and administration of study intervention are provided in the Pharmacy Manual.

Duration of Treatment and Follow-up:

Screening: Completed within 28 days prior to the Day 1 Visit.

Double-Blind Treatment Period (Day 1 through [redacted] Study treatment (daxdilimab or placebo) is administered SC [redacted] with an additional dose [redacted], all participants will be assigned to a quarterly dosing maintenance regimen based upon the renal response observed at [redacted] and will either receive daxdilimab or placebo [redacted] (last dose administered at [redacted]). Final evaluation will occur at [redacted].

End-of-Study/Early Termination Visit: Week 112 or earlier if the participant withdraws consent to participate in the trial.

Safety Follow-Up: Participants should be followed to assess AE/SAEs for at least 12 weeks after the last study intervention administration, approximately 4, 8, and 12 weeks after the last study intervention dose, unless the participant withdraws consent. Participants who do not agree to in-person follow-up site visits will be contacted (through telehealth visits – video call/phone/email) to assess AE/SAEs, unless the participants withdraw consent. Assessments will include of any AE/SAEs that have occurred within the last 4 weeks and will confirm if any previous AE/SAEs have resolved.

Criteria for Evaluation:

Efficacy:

Name of Sponsor/Company:	**Name of Investigational Product:**	**Name of Active Ingredient:**
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Efficacy will be assessed by renal responses, change in proteinuria, and GFR.

Participant's experience will be assessed by the Patient Global Assessment (PtGA) and the Patient Global Impression of Change (PGI-C) scales.

Pharmacokinetics, Pharmacodynamics, and Immunogenicity

The PK of daxdilimab will be assessed by serum PK concentrations.

Daxdilimab immunogenicity will be assessed by the rate and titer of ADA.

[redacted]

Safety:

Safety will be assessed and will include monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, and monitoring of hematology, blood chemistry, and urinalysis.

Statistical Analysis on Efficacy and Safety Parameters

Efficacy Analyses

Analyses of the Primary Efficacy Endpoint:

The proportion of participants achieving CRR at Week 48 and sustained through Week 52 in the daxdilimab group will be compared to that of the placebo group using a logistic regression model with treatment, baseline eGFR value and baseline UPCR value included in the model.

Analyses of the Secondary Efficacy Endpoints:

ORR at Week 48 and sustained through Week 52 will be analyzed using a logistic regression model with treatment, baseline eGFR value and baseline UPCR value included in the model. Response in sustained reduction of OCS dose will be analyzed similarly using a logistic regression model with treatment, randomization stratification factor and baseline OCS dose included in the model.

Change from baseline in eGFR at Week 52 will be analyzed using mixed models for repeated measures (MMRM) with treatment, visit, visit by treatment interaction, randomization stratification factor (UPCR only) and baseline eGFR value included in the model.

Safety Analyses

AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants reporting TEAEs will be summarized for each treatment group by MedDRA System Organ Class and preferred terms (PT), by severity, and by relationship to the study intervention. The number and percentage of participants reporting TESAEs and TEAESIs will also be summarized.

Other safety parameters, including but not limiting to laboratory assessments and vital signs will also be summarized as appropriate.

Pharmacokinetic Analyses

Name of Sponsor/Company:	**Name of Investigational Product:**	**Name of Active Ingredient:**
Horizon Therapeutics Ireland DAC	Daxdilimab (HZN-7734)	Daxdilimab (HZN-7734)

Serum concentrations will be summarized descriptively by treatment and by visit.

[redacted]/Immunogenicity Analyses

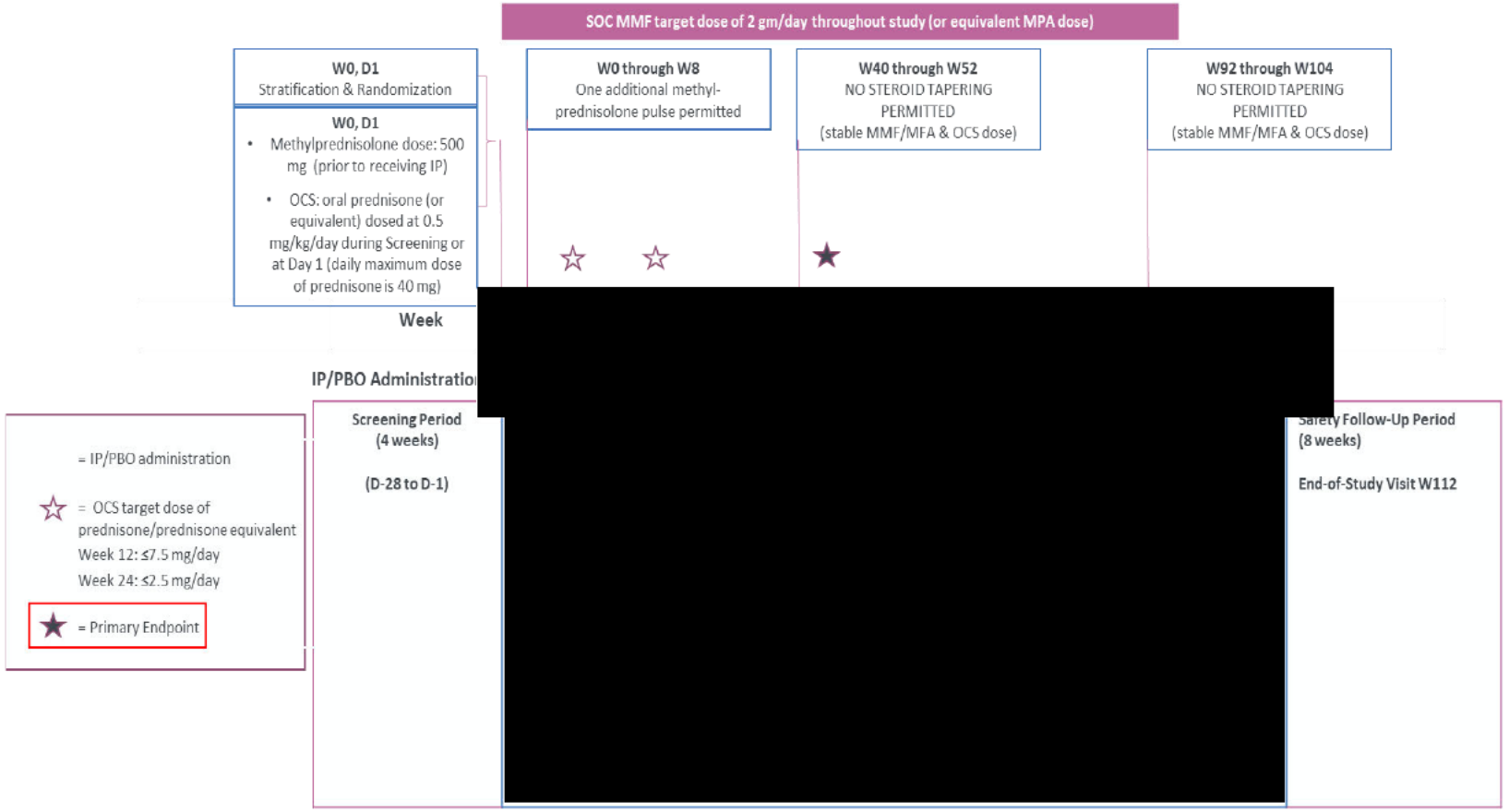
[redacted] rate of positive ADA and ADA titer will be summarized descriptively by treatment and by visit.

Sample Size Estimate

A sample size of approximately 210 participants (up to approximately 70 participants per treatment group) is planned for this trial. The sample size was calculated based on the primary efficacy endpoint. Assuming a placebo response rate of 25%, 70 participants per treatment group will provide approximately 80% power to detect an increase in response of 20% in a daxdilimab group as compared to the placebo group at the 2-sided alpha level of 0.10 using a Chi-square test. The minimum detectable difference is 13% between the daxdilimab group and placebo group. The assumption of 25% responder rate for placebo is based upon published results (Mejia-Vilet et al, 2021).

1.2. Schema

Figure 1 Trial Diagram



CRR = complete renal response; D = day; IP = investigational product; MMF = mycophenolate mofetil; MPA = mycophenolic acid; OCS = oral corticosteroids; PRR = partial renal response; [redacted] SC = subcutaneously; SFU = Safety Follow-Up; SOC = standard-of-care; W = week.

1.3. Schedule of Activities (SoA)

Table 2 and Table 3 summarize the Screening and treatment assessments and procedures for the first year of the trial and Table 4 summarize the treatment and follow-up procedures and assessments for the second year of the trial.

Table 2 Screening Procedures and Assessments

Period	**Screening Period**
Study Day	**-28 to -1**
Visit Number	**1**
General	
Informed consent	X
Inclusion/exclusion criteria review	X
Renal biopsy [a]	See footnote [a]
EULAR/ACR SLE classification criteria	X
Demographic data	X
Medical/Surgical/SLE/LN history	X
TB assessment [b]	X
Physical examination [c]	X
Vital signs, height, and weight [d]	X
12-lead ECG (after 10 minutes rest in supine position) [e]	X
Laboratory Assessments	
[redacted]	[redacted]
24-hour UPCR	X
Pregnancy (serum β-hCG) test (in women of childbearing potential)	X
FSH (to confirm postmenopausal status, as appropriate) [f]	X
Serum virology [g]	X
Routine chemistry [h]	X
Hematology (CBC with differential)	X
HbA1c	X
Lipid profile [i]	X
Urinalysis [j]	X
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Safety	
Concomitant medications [k]	X
AEs, SAEs, and/or AESIs	X

Table 2 Screening Procedures and Assessments

Period	**Screening Period**
Study Day	**-28 to -1**
Visit Number	**1**

ACR = American College of Rheumatology; AE = adverse event; AESI = AE of special interest; [redacted]; βhCG = β-human chorionic gonadotropin; [redacted] CBC = complete blood count; [redacted] ECG = electrocardiogram; EULAR = European League Against Rheumatism; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; [redacted]; LN = lupus nephritis; [redacted] SAE = serious AE; SLE = Systemic Lupus Erythematosus; [redacted] TB = tuberculosis; UPCR = urine protein to creatinine ratio; X = to be performed.

[a] A local biopsy report indicating active, proliferative lupus nephritis will be used to confirm participant eligibility. Availability of the Screening biopsy sample (tissue, slides, or digital pathology images) for adjudication submission must also be confirmed. If a participant has not had a recent kidney biopsy within the 6 months prior to Screening, one may be performed to assess eligibility for the study provided informed consent has been given and the local biopsy report is received prior to Randomization. If a renal biopsy is performed as part of standard of care after Randomization, the results will be recorded in the electronic case report form.

[b] The results of an IFN-gamma release assay (ie, QuantiFERON-TB Gold Plus or TSPOT) performed within 12 weeks of the Screening Visit (if available) are acceptable, provided there is no reason to suspect any re-exposure.

[c] A complete physical examination including assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.

[d] Vital signs include systolic and diastolic blood pressure obtained after at least 5 minutes at rest in a seated position, heart rate, respiratory rate (breaths/min), and body temperature. Height will be measured at Screening only.

[e] Should be performed after vital signs are collected.

[f] FSH testing does not have to be repeated if performed within 12 weeks prior to Screening (eg, re-screening).

[g] Includes human immunodeficiency virus testing, hepatitis B testing (hepatitis B surface antigen and hepatitis core antibody [HBcAb] Serum virology does not have to be repeated if performed within 12 weeks prior to Screening (eg, re-screening).

[h] Refer to the Laboratory Manual for a complete list of routine laboratory assessments.

[i] Participants must be fasting for at least 8 hours when lipid profiles are obtained. Visit recommended to occur in the morning.

[j] Urine collection can be postponed for up to 14 days in women with menstrual bleeding or a urinary tract infection at the scheduled visit. Refer to the Laboratory Manual for a complete list of routine urinalysis assessments.

[k] [redacted]

[l] Use of anti-proteinuric agents (eg, ACEI/ARBs) are allowed during the study if they had been started at least 10 days prior to the assessment of the second screening 24-hour UPCR sample (ie, the first sample for 24 hour UPCR is collected at the start of the screening process and the second sample is collected within 14 days prior to the expected date of Randomization).

Table 3 First Year Treatment Procedures and Assessments

Period	**Treatment Period**														
Study Week	[redacted]														
Study Day															
Visit Window (± Days)	**-**	**3**	**3**	**5**	**5**	**5**	**5**	**5**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Eligibility review [a]	X														
Physical examination [b]	X				X			X			X				X
Weight	X				X			X			X				X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (after 10 minutes rest in supine position) [d]								X							X
Randomization [e]	X														X
[redacted]	■				■			■			■				■
[redacted]	■				■			■			■				■
SLICC/ACR Damage Index (SDI)	X							X							X
[redacted]	■		■		■			■			■				■
[redacted]	■		■		■			■			■				■
[redacted]			■		■			■			■				■
Pregnancy (urine) test [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
24-hour UPCR [h]	X				X			X			X			X	X
Routine chemistry [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology (CBC with differential)	X				X			X			X			X	X
Lipid profile [j]	X							X							X
Urinalysis [k]	X				X			X			X			X	X
[redacted]	■				■			■			■			■	■
[redacted]	■				■			■			■			■	■
[redacted]	■		■		■			■			■			■	■
[redacted]	■		■		■			■			■			■	■

Table 3 First Year Treatment Procedures and Assessments

Period	Treatment Period														
Study Week	[redacted]														
Study Day															
Visit Window (± Days)	-	3	3	5	5	5	5	5	7	7	7	7	7	7	7
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
[redacted]	■		■		■			■			■			■	■
[redacted]	■		■					■						■	■
CCI [redacted]	■		■		■			■			■			■	■
[redacted]	■		■					■							■
Daxdilimab PK (serum) [m]	X	X	X	X	X	X	X	X			X			X	X
Daxdilimab ADA [n]	X		X		X			X			X			X	X
[redacted]	■		■		■			■			■			■	■
[redacted]	■ ■		■					■						■	■
[redacted]	■							■							■
Screening biopsy sample shipment for adjudication [p]		X													
[redacted]								[redacted]							
Study treatment administration	[redacted]														
Local injection site assessment															
MMF/MPA/OCS dispensing [r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IV methylprednisolone administration [s]	X														
Oral corticosteroid reduction (tapering)		X	X	X	X	X	X		X	X	X	X			
Concomitant medications [t]	← Continuous →														
AEs, SAEs, and/or AESIs [u]	← Continuous →														

ADA = antidrug antibody; AE = adverse event; AESI = AE of special interest; CBC = complete blood count; ECG = electrocardiogram; [redacted] IP = investigational product; MMF = mycophenolate mofetil; MPA = mycophenolic acid; mSFI = modified [redacted]; [redacted] OCS = oral corticosteroids; [redacted] PK = pharmacokinetics; [redacted] SAE = serious AE; [redacted]; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; [redacted] X = to be performed.

[a] Participant eligibility (based on Screening assessments, including non–laboratory-based assessments at Baseline [Day 1] as per the inclusion and exclusion criteria) must be checked again on Day 1 prior to Randomization.

[b] Focused physical examination including assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.

[c] Vital signs include systolic and diastolic blood pressure obtained after at least 5 minutes at rest in a seated position, heart rate, respiratory rate (breaths/min), and body temperature.

[d] Should be performed after vital signs are collected.

[g] Women of childbearing potential or women who are postmenopausal for less than 2 years.

[h] 24-hour urine collection should begin 2 days prior to the scheduled study visit in order not to coincide with the sampling due on the day of the study visit.

[i] Refer to the Laboratory Manual for a complete list of routine laboratory assessments.

[j] Participants must be fasting for at least 8 hours when lipid profiles are obtained. Visit recommended to occur in the morning.

[k] Urine collection can be postponed for up to 14 days in women with menstrual bleeding or a urinary tract infection at the scheduled visit. Refer to the Laboratory Manual for a complete list of routine urinalysis assessments.

[m] Blood samples will be collected in serum separator collection tubes to evaluate PK at the following visits: pre- and 6 hours (± 1 hour) post-injection on Day 1, prior to SC administration on a single sample will be collected at the End-of-Study Visit.

[n] Daxdilimab immunogenicity will be assessed by the incidence and titer of anti-drug antibodies prior to the daxdilimab administration.

[p] The submission of the Screening biopsy sample (tissue block, slides, or digital pathology images) for adjudication should be provided within 2 months post-randomization.

[r] For participants not on MMF or MPA during Screening, MMF/MPA therapy will start on Day 1 (Baseline – Visit 2). A quantity sufficient for a 12-week supply should be dispensed at Week 52.

[s] IV methylprednisolone administered 500 mg on Day 1 (Baseline – Visit 2). If IV corticosteroids must be administered during Screening, then the specimens will be collected prior to the infusion.

[t] At each visit, use of any rescue therapy for worsening LN and restricted or prohibited medication beyond the protocol allowed threshold will also be assessed.

[u] Participants who choose to discontinue study intervention will be contacted (either in-person at the site or through telehealth visits – video call/phone/email), if participant agrees, to assess AE/SAEs approximately 4, 8, and 12 weeks after last study intervention dose. Assessments will include of any AE/SAEs that have occurred within the last 4 weeks and will confirm if any previous AE/SAEs have resolved.

Table 4 Second Year Treatment and Follow-Up Procedures and Assessments

Period	**Treatment Period**													**Safety Follow-**
Study Week	[redacted]													
In-Clinic Visit			**X**			**X**			**X**			**X**	**X**	**X**
Telephone or Telehealth Visit [a]	**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**			
Visit Window (± Days)	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Visit Number	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30 (End-of-Study or Early Termination)**
Physical examination [b]			X			X			X			X	X	
Weight			X			X			X			X	X	X
Vital signs [c]			X			X			X			X	X	X
12-lead ECG (after 10 minutes rest in supine position) [d]						X							X	X
Pregnancy (urine) test [e]			X			X			X			X	X	X
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
24-hour UPCR [f]			X			X			X			X	X	
Routine chemistry [g]			X			X			X			X	X	X
Hematology (CBC with differential)			X			X			X			X	X	X
Lipid profile [h]						X							X	
Urinalysis [i]			X			X			X			X	X	X
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]						[redacted]				[redacted]	
Daxdilimab PK (serum) [l]			X			X			X			X	X	X

Table 4 Second Year Treatment and Follow-Up Procedures and Assessments

Period	**Treatment Period**													**Safety Follow-Up Period**
Study Week	[redacted]													
In-Clinic Visit			**X**			**X**			**X**			**X**	**X**	**X**
Telephone or Telehealth Visit [a]	**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**			
Visit Window (± Days)	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Visit Number	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30 (End-of-Study or Early Termination)**
Daxdilimab ADA [l]			X						X					X
[redacted]			[redacted]			[redacted]			[redacted]				[redacted]	[redacted]
[redacted]			[redacted]						[redacted]				[redacted]	[redacted]
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
SLICC/ACR Damage Index (SDI) [m]						X							X	X
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
[redacted]		[redacted]												
Study treatment administration	[redacted]													
Local injection site assessment														
MMF/MPA/OCS dispensing [q]			X			X			X			X		
Oral corticosteroid reduction (discontinuation) [r]			X											
Concomitant medications [s]	←							Continuous					→	
AEs, SAEs, and/or AESIs [t]	←							Continuous					→	

ADA = antidrug antibody; AE = adverse event; AESI = AE of special interest; CBC = complete blood count; ECG = electrocardiogram; EOT = end-of-treatment; IFN = interferon;IP = investigational product; MMF = mycophenolate mofetil; MPA = mycophenolic acid; [redacted] OCS = oral corticosteroids; [redacted] PK = pharmacokinetics; [redacted] SAE = serious AE; [redacted] SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; [redacted] X = to be performed.

[a] During the second year, participants are not required to visit the clinical site at Weeks 56, 60, 68, 72, 80, 84, 92, and 96; applicable assessments may instead be performed as a telehealth visit – video call or phone call with the participant (ie, OCS reduction, concomitant medication, and adverse event review), unless an in-person site visit is clinically indicated.

[b] Focused physical examination including assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.

[c] Vital signs include systolic and diastolic blood pressure obtained after at least 5 minutes at rest in a seated position, heart rate, respiratory rate (breaths/min), and body temperature.

[d] Should be performed after vital signs are collected.

[e] Women of childbearing potential or women who are postmenopausal for less than 2 years.

[f] 24-hour urine collection should begin 2 days prior to the scheduled study visit in order not to coincide with the [redacted] sampling due on the day of the study visit.

[g] Refer to the Laboratory Manual for a complete list of routine laboratory assessments.

[h] Participants must be fasting for at least 8 hours when lipid profiles are obtained. Visit recommended to occur in the morning.

[i] Urine collection can be postponed for up to 14 days in women with menstrual bleeding or a urinary tract infection at the scheduled visit. Refer to the Laboratory Manual for a complete list of routine urinalysis assessments.

[redacted]

[k] Blood samples will be collected in serum separator collection tubes to evaluate PK at the following visits: pre- and 6 hours (± 1 hour) post-injection on Day 1, prior to SC administration on [redacted]; a single sample will be collected at the End-of-Study Visit.

[l] Daxdilimab immunogenicity will be assessed by the incidence and titer of anti-drug antibodies prior to the daxdilimab administration.

[m] May be completed more frequently if clinically indicated.

[redacted]

[p] Additional follow-up after Week 100 will be performed for any ongoing injection site reactions during the SFU Period.

[q] A quantity sufficient for a 12-week supply should be dispensed at Weeks 64, 76, 88, and 100.

[r] Continued tapering of OCS is recommended for all participants after the Week 52 Visit with the goal of achieving discontinuation (ie, 0 mg) by Week 76. Due to variability in participant responses to OCS treatment and tolerability of taper, Investigators will have flexibility of when the OCS dose is reduced at each visit.

[s] At each visit, use of any rescue therapy for worsening LN and restricted or prohibited medication beyond the protocol allowed threshold will also be assessed.

[t] Participants who choose to discontinue study intervention will be contacted (either in-person at the site or through telehealth visits – video call/phone/email), if participant agrees, to assess AE/SAEs approximately 4, 8, and 12 weeks after last study intervention dose. Assessments will include of any AE/SAEs that have occurred within the last 4 weeks and will confirm if any previous AE/SAEs have resolved.

2. INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of unknown etiologies. Lupus nephritis (LN) is the most common major organ manifestation of SLE. It affects approximately 31-60% of lupus patients and is more prevalent in certain ethnic groups, such as African Americans, Asians, and Hispanics (Borchers et al, 2010; Hanly et al, 2016; Mahajan et al, 2020; Anders et al, 2020). Although renal outcomes have improved with the introduction of immunosuppressive treatment, LN still represents a major risk factor for the long-term outcome of patients with SLE and adversely affects the prognosis, as measured by patient and renal survival rates as well as quality of life and work disability (Furst et al, 2013; Li et al, 2009; Mok et al, 2013; Pelletier et al, 2009; Parikh et al, 2020). Renal survival rates (ie, survival without dialysis) in recent studies ranged from 83% to 92% at 5 years of follow-up and from 74% to 84% at 10 years of follow-up (summarized in Mok et al, 2013). The risk of end-stage renal disease (ESRD) is particularly high in patients with diffuse proliferative glomerulonephritis (reviewed in Mok et al, 2013). Several studies have shown that the standardized mortality ratio of patients with LN is 6-9-fold higher compared to the general population and about 3-fold higher compared to patients with non-renal SLE (reviewed in Mok et al, 2013; Hanly et al, 2016). The mortality rate increases with accumulation of renal damage and is highest in LN patients with ESRD. The life expectancy of SLE patients with renal disease and those with renal damage is reduced by approximately 15 years and 23 years, respectively, compared to the general population (Mok et al, 2013). Lupus nephritis is also a major factor contributing to SLE related hospitalizations and overall health care costs (Furst et al, 2013; Li et al, 2009; Pelletier et al, 2009; Thompson et al, 2021).

2.1. Background

There is substantial unmet medical need in the treatment of LN, particularly for patients with proliferative LN. Belimumab and voclosporin have recently been approved for LN (Mejia-Vilet et al, 2021) but real world and long-term experience with these drugs is not yet available. Various other treatment regimens are widely used as local standards of care. The standard treatment for proliferative LN consists of 6 to 12 months of intensive immunosuppressive therapy (usually either mycophenolate mofetil [MMF] or cyclophosphamide with corticosteroids) followed by a longer period of less intensive maintenance therapy (Bertsias et al, 2012; Hahn et al, 2012; Fanouriakis et al, 2020). Corticosteroid dosing frequently includes pulse intravenous (IV) methylprednisolone (500 mg to 1,000 mg/day for 1-3 days) followed by daily oral glucocorticoids (0.3 to 0.5 mg/kg/day of prednisone-equivalent) with a goal of reducing the dose to around ≤7.5 mg/day of prednisone-equivalent by 3 to 6 months. MMF is the recommended agent by the American College of Rheumatology (ACR) (Hahn et al, 2012) and the European League Against Rheumatism (EULAR) (Bertsias et al, 2012; Fanouriakis et al, 2020) with a total daily dose of 2 to 3 gm/day orally for 6 months, followed by an extended period of treatment with lower doses of MMF.

Two regimens of IV cyclophosphamide are recommended as alternatives: 1) low-dose “Euro Lupus” cyclophosphamide (500 mg IV once every 2 weeks×3 months), followed by maintenance therapy with daily oral azathioprine or daily oral MMF or 2) high-dose cyclophosphamide

(500 to 1000 mg/m^2 IV once a month×6 months), followed by maintenance treatment with MMF or azathioprine.

Maintenance therapy is recommended for a minimum of 12 months with lower intensity immunosuppression with or without low-dose corticosteroids (≤7.5 mg/day). Mycophenolate mofetil (≤2 gm/day) or azathioprine are the most commonly used agents for maintenance (Bertsias et al, 2012;Fanouriakis et al, 2020; Hahn et al, 2012; Radhakrishnan et al, 2012;).

In this study, MMF was chosen as standard-of-care (SOC) background therapy. While the target dose of MMF recommended by various management guidelines (ACR, EULAR, and KDIGO) is 2 to 3 gm/day orally for 6 months followed by an extended period of treatment with lower doses of MMF, several studies in Asian and Caucasian LN populations have shown doses ≤2 gm/day lead to similar renal responses but a lower frequency of adverse events (AEs) compared to doses of 3 gm/day (Chan, 2012; Li et al, 2012; Mulic-Bacic et al, 2008; Ong et al, 2005). Consistent with these observations, the ACR guidelines recommend a target of 2 gm/day for induction in Caucasian patients with LN (Hahn et al, 2012), which is the higher end of the range used for induction in Asian countries. Although a higher target dose is frequently used in patients of African descent, there is no evidence to support this distinction.

Multiple lines of evidence indicate a role of plasmacytoid dendritic cells (pDCs) and type I IFN in the pathogenesis of SLE and LN. For example, type I IFN and proteins induced by type I IFN have been associated with greater disease activity and organ system involvement in SLE and LN (Bengtsson et al, 2000; Dall'Era et al, 2005; Kirou et al, 2005;). High serum levels of type I IFN have been associated with high anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody titers, LN, and progressive skin rashes (Bengtsson et al, 2000).

The disease pathogenesis of SLE includes activation of innate immunity, with increased production of type I IFN, including IFN-α, and increased number of pDCs and myeloid dendritic cells in involved tissue (Baechler et al, 2003; Banchereau et al, 2004; Bengtsson et al, 2000; Crow, 2010; Crow and Wohlgemuth, 2003; Dall'Era et al, 2005; Rönnblom and Alm, 2003). Specific humoral and cellular immune systems are activated. Autoantibodies are universally present and may precede development of clinically apparent disease by many years (Arbuckle et al, 2003). Systemic lupus erythematosus-associated autoantibodies include anti-dsDNA, anti-nucleosomes, anti-ribonucleoprotein (anti-RNP) complex, and anti-Smith antibodies (Rahman and Isenberg, 2008). Immune complexes containing anti-dsDNA or anti RNP antibodies can activate type I IFN production by plasmacytoid dendritic cells (Bengtsson et al, 2000; Rönnblom and Alm, 2003).

A potential role of pDCs in the pathogenesis of LN has been suggested by both animal and human data. Systemic IFN-α accelerated LN in several murine models (Fairhurst et al, 2008, Liu et al, 2011). Additionally, a type I interferon response was induced in lupus-prone mice treated with a synthetic double-stranded RNA ligand, which was accompanied by high titers of anti-dsDNA antibodies, increased immune complex deposition, increased metalloproteinase activity, and accelerated LN and death (Triantafyllopoulou et al, 2010). pDCs are the most potent producers of type I IFNs (Baccala et al, 2013) and pDCs from mice susceptible to developing lupus-like disease demonstrate an increased capacity to produce type I IFNs after TLR9 stimulation (Klarquist et al, 2016) suggesting that pDCs, and the type I IFNs they produce, may play a key role in the pathogenesis of lupus in these models. Indeed, when pDCs were depleted

in lupus-prone mice there were marked reductions in type I IFN, interferon gene signature, autoantibody production, and the severity of kidney pathology (Baccala et al, 2013; Klarquist et al, 2016; Rowland et al, 2014).

In humans, a role for pDCs and IFN-α in the LN disease process has been suggested by several studies. For example, the formation of endothelial cell tubuloreticular inclusions found in LN is thought to be driven by type I IFN, and other than in LN, they can only be seen in viral and IFN-induced nephropathies (Anders et al, 2014). Elevated serum IFN-induced chemokine levels were strongly associated with the risk of renal flare (Bauer et al, 2009) and urine IFN-induced chemokines have been proposed as biomarkers for active LN (Aragon et al, 2020; Manoharan et al, 2010). The type I gene signature is increased in the glomeruli of a subset of LN patients (Peterson et al, 2004) and cross-sectional studies showed a positive correlation between the blood IFN signature and active LN or risk of renal flare (Feng et al, 2006; Landolt-Marticorena et al, 2009). Plasmacytoid dendritic cells are the main producers of type I IFN in SLE. In LN patients, there are decreased frequencies of pDCs in the blood and increased numbers in the kidneys (Tucci et al, 2008) suggesting that pDCs are recruited from the circulation to areas of active inflammation in the kidney (Baccala et al, 2013). pDCs are mostly localized in the tubulointerstitial area of LN kidneys with increased infiltrate seen in patients with class III-IV disease (Fiore et al, 2008). In severe tubulointerstitial inflammation, pDCs are associated with increased T cell infiltration and can contribute further to local inflammation by presenting antigen to CD4+ T cells (Liarski et al, 2019).

Together, these pre-clinical and clinical data strongly support the hypothesis that pDCs, and their production of type I IFNs, are involved in the immunopathogenesis of LN; therefore, depleting pDCs with daxdilimab may be a novel and efficacious therapy for the treatment of LN.

2.1.1. Trial Rationale

Daxdilimab (previously known as MEDI7734, VIB7734, and HZN-7734) is an IgG1 lambda (IgG1λ) afucosylated monoclonal antibody (mAb) specific for immunoglobulin-like transcript 7 (ILT7), a cell-surface protein that is unique to pDCs in human and the nonhuman primate. Daxdilimab binds to ILT7 on the surface of pDCs, which leads to the recruitment of macrophages and natural killer cells, thus inducing apoptosis and depletion of pDCs in vivo. The afucosylation of daxdilimab is designed to enhance the potency of daxdilimab for antibody-dependent cellular cytotoxicity against pDCs. Since pDCs are the major cell type that secretes type I IFNs in response to nucleic acid-containing immune complexes, it is hypothesized that depletion of pDCs will reduce disease activity for patients with autoimmune diseases that are partially driven by abnormally high levels of type I IFNs.

Data from a Phase 2 trial with another type-1-IFN-blocking agent have demonstrated improvement in LN disease activity, supporting the rationale for blocking the IFN pathways and pDCs in patients with proliferative LN (Jayne et al, 2021). Given the lack of highly efficacious and safe treatments for active proliferative LN and the significant morbidity and increased mortality associated with LN, there is currently a significant unmet need for new targeted therapies in this indication. Based on its mechanism of action of pDC depletion, daxdilimab has the potential to decrease LN disease activity. In addition, based on data currently available, daxdilimab presents an acceptable safety profile, and hence it is justified to evaluate its potential efficacy in patients with active proliferative LN.

2.2. Risk/Benefit Assessment

2.2.1. Known Potential Risks

Daxdilimab was tested in a first-in-human, single-ascending dose study (Study D6080C00001). The key objectives of the study were to evaluate the single dose safety, pharmacokinetics (PK), and pharmacodynamics (PD). The study enrolled 36 adult subjects with dermatomyositis (DM), polymyositis (PM), Sjogren's syndrome, systemic lupus erythematosus (SLE), or systemic sclerosis. Subjects received a single subcutaneous (SC) injection of daxdilimab 1, 5, 15, 50, or 150 mg, or placebo. After single SC administration, serum peak concentrations were observed 5 to 8 days post-dose. Daxdilimab PK exposures increased in an approximately dose-proportional manner. Apparent clearance (CL/F) ranged from 0.468 to 1.03 L/day. Apparent volume of distribution (Vz/F) ranged from 9.89 to 19.0 L. The estimated terminal elimination half-life ($t_{1/2}$) ranged from 13 to 20 days across dose levels. No serious adverse events (SAEs) occurred that were considered related to the investigational product (IP). Two subjects had treatment-emergent adverse events (TEAEs) considered related to the IP by the Investigator: one subject in the placebo group with nausea (Grade 1) and one subject in the daxdilimab 50 mg group with tongue discolouration (Grade 1). The most common adverse events (AEs) reported in the daxdilimab-treated subjects were diarrhoea (11.5%) and upper respiratory tract infection (11.5%). There was no imbalance of AEs between the daxdilimab and placebo groups. No injection site reactions or hypersensitivity reactions were reported. No anti-drug antibodies (ADAs) occurred. Mean reductions of at least 50% in the pDC level of daxdilimab-treated subjects were evident at 24 hours after dosing in all dose groups. Increasing doses were associated with a non-linear increase in pDC reduction. Increasing doses were generally associated with a longer duration of pDC reduction.

Study HZN7734.P1b.S1 evaluated the PK, PD, and safety of 3 monthly doses of daxdilimab. The study enrolled 31 subjects with SLE, cutaneous lupus erythematosus (CLE), Sjogren's syndrome, systemic sclerosis, PM, or DM. Subjects received placebo or daxdilimab at 5, 50, and 150 mg by SC injection. Daxdilimab PK exposure was approximately dose proportional over the dose range investigated. Apparent steady-state clearance (CLss/F) values were similar across dose groups and ranged from 0.62 to 1.18 L/day. The $t_{1/2}$ was 14.6 days for subjects receiving 150 mg daxdilimab. Sixteen of 22 (72.7%) daxdilimab-treated subjects and 6 of 9 (66.7%) placebo treated subjects experienced at least one TEAE. There were no deaths in the trial. One placebo-treated subject and no daxdilimab-treated subjects experienced treatment emergent SAEs. No subject experienced an AE leading to treatment discontinuation. No treatment-emergent ADA was observed in subjects treated with daxdilimab. In subjects with CLE, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity (CLASI-A) scores improved more in the daxdilimab 150 mg group than the placebo group. After 3 monthly SC doses of daxdilimab 50 mg or 150 mg, the median change in percent pDCs at Day 85 was -54.1% in the daxdilimab group, compared to a +9.8% in the placebo group.

To date, no adverse drug reactions (ADRs) for daxdilimab have been identified. Important potential risks for daxdilimab include viral infection and viral reactivation, opportunistic infection, malignancy (other than non-melanoma skin cancer), and hypersensitivity reactions including anaphylaxis. Other potential risks include injection site reactions, vaccine interaction, drug-drug interactions, and reproductive toxicity.

2.2.2. Known Potential Benefits

In this Phase 2 trial, it is hypothesized that participants with active, proliferative LN may see an improvement in their condition as a result of participating in the trial.

Participation in this trial may help generate future benefit for larger groups of patients with LN if daxdilimab proves to be successful in treating this disease.

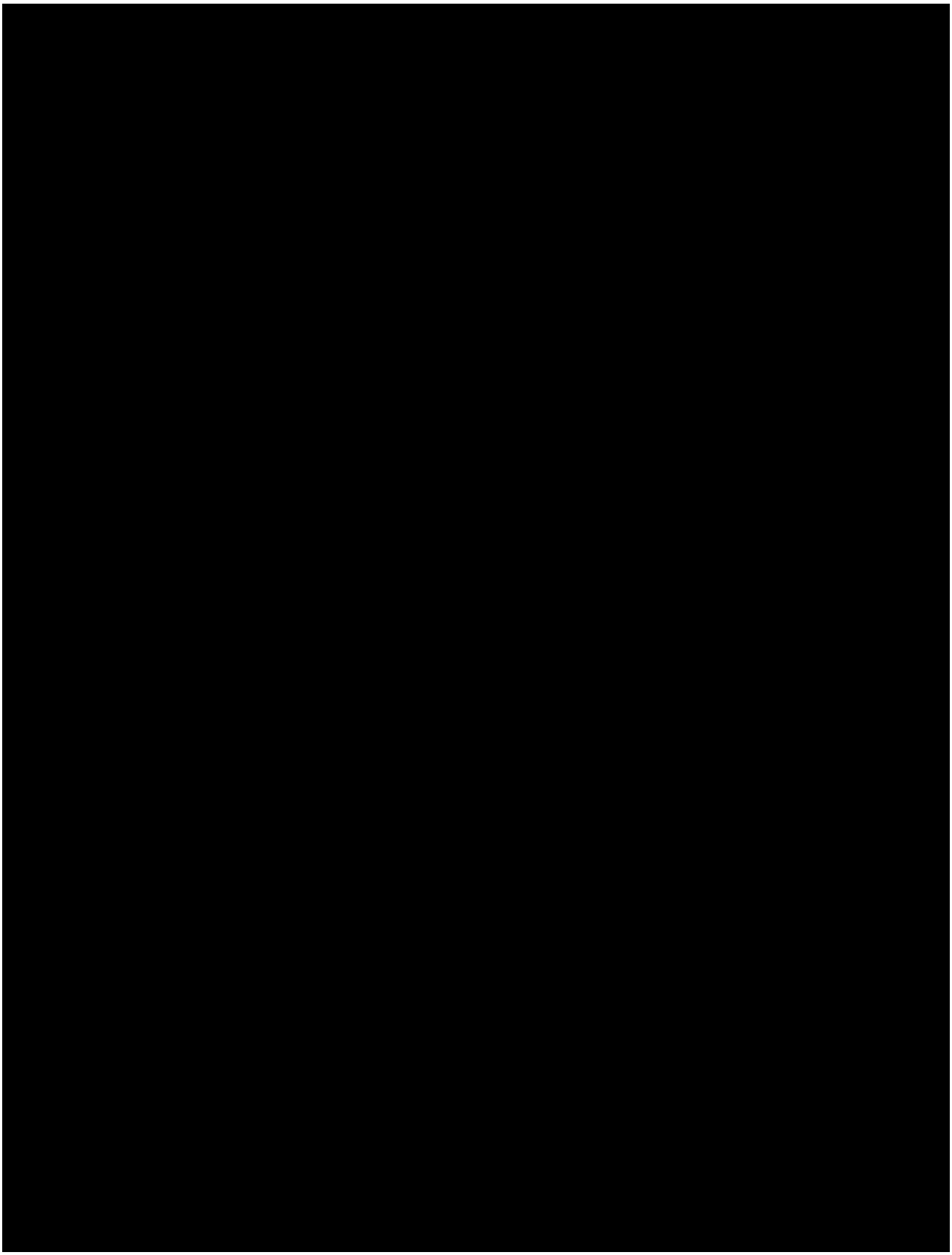
2.2.3. Overall Benefit Risk Conclusion

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical and clinical studies are considered sufficient to expect a positive benefit/risk assessment for the treatment of patients with active, proliferative LN with daxdilimab, and therefore to initiate this trial.

3. OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of daxdilimab in combination with SOC compared to placebo in combination with SOC in participants with active, proliferative LN.	Proportion of participants achieving Complete Renal Response (CRR) at [redacted] CRR is defined as meeting all of the following: • Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m^2 or no worse than 15% below baseline • 24-hour UPCR ≤ 0.5 mg/mg • No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment
Secondary Objectives	**Secondary Endpoints**
To assess overall renal response (ORR) (defined as CRR plus partial renal response [PRR]) with daxdilimab versus placebo in participants with active, proliferative LN.	Proportion of participants achieving ORR at [redacted] See above for definition of CRR. PRR is defined as meeting all of the following: • eGFR ≥ 60 mL/min/1.73m^2 or no worse than 15% below baseline • Improvement in 24-hour UPCR: – For participants with a baseline UPCR ≤ 3.0 mg/mg: < 1.0 mg/mg – For participants with a baseline UPCR > 3.0 mg/mg: > 50% improvement from baseline and ≤ 3.0 mg/mg • No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment
To assess the change from baseline in eGFR with daxdilimab versus placebo in participants with active, proliferative LN.	• Change from baseline in eGFR at Week 52.

To evaluate the ability to improve dose requirements of oral corticosteroids (OCS) with daxdilimab versus placebo in participants with active, proliferative LN.	Proportion of participants able to taper OCS to ≤ 2.5 mg/day prednisone-equivalent by Week 24 and maintain this dose through Week 52. Sustained reduction of OCS dose: • Prednisone-equivalent dose ≤ 2.5 mg/day by Week 24 and not exceeding this dose through Week 52 and • No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment
To characterize the PK and immunogenicity of daxdilimab in participants with active, proliferative LN.	• Serum concentration of daxdilimab. • Rate of ADA directed against daxdilimab and ADA titer for the duration of the study.
To evaluate the safety and tolerability of daxdilimab in combination with SOC in participants with active, proliferative LN.	• Incidence of treatment-emergent adverse events (TEAEs). • Incidence of treatment-emergent serious adverse events (TESAEs). • Incidence of treatment-emergent AEs of special interest (TEAESIs): hypersensitivity reaction, including anaphylaxis, severe (Grade 3 or higher) viral infection/reactivation, herpes zoster, opportunistic infection, and malignancy (except non-melanoma skin cancer).



4. STUDY DESIGN

4.1. Overall Design

This trial is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to assess the efficacy and safety of daxdilimab in patients with active, proliferative lupus nephritis despite standard of care. An overview of the trial design is presented in the schematic provided in Section 1.2 and details of trial activities are provided in Section 1.3.

Approximately 210 participants will be randomized in a ratio of 1:1:1 (70 participants per group) to receive either daxdilimab [redacted] mg or [redacted] mg SC or placebo SC in addition to SOC background therapy as described below in Table 5. Randomization will be stratified by:

- Pre-randomization urine protein to creatinine ratio (UPCR) < 3.0 mg/mg vs. ≥ 3.0 mg/mg
- Screening eGFR < 60 mL/min/1.73m^2 vs. ≥ 60 mL/min/1.73m^2

Table 5 First Year Treatment Assignment

Group	[redacted]
1	
2	
3	

[redacted]

Table 6 Second Year Treatment Assignment

Group	[redacted]
1	
2	
3	

Participants may enter the study taking daily OCS at a maximum dose of 0.5 mg/kg/day of prednisone-equivalent, not to exceed 40 mg/day, and must be on a stable dose for at least 10 days prior to Randomization. In addition, participants will receive IV methylprednisolone pulse 500 mg on the day of Randomization, prior to receiving the study intervention, unless they received a methylprednisolone pulse of ≥ 500 mg within 10 days prior to Randomization followed by a reducing taper of OCS for participants already taking OCS prior to entry.
For participants who are not already taking prescribed MMF prior to Randomization, the dosing of MMF will start at 500 mg twice a day (BID) for a total daily dose of 1 gm/day for the first week, increasing to 1 gm BID for a total daily dose of 2 gm/day for the second and subsequent weeks (ie, beginning on Day 8). Prior to initiation of MMF, please refer to the restricted medications section in prior and concomitant therapy criteria because of potential interaction with MMF. An equivalent dose of mycophenolic acid (MPA) may be used as an alternative to MMF.

This trial will comprise a Screening Period of approximately 4 weeks (Days -28 to -1), a Treatment Period with Randomization on Day 1 followed by treatment through [redacted] totaling [redacted] Under exceptional circumstances such as delayed laboratory results, drug washout, or the impact of COVID-19, the Screening Period may be increased by 2 weeks, upon approval by the Medical Monitor. In general, re-screening of participants may occur only in consultation with and approval by the Medical Monitor. The trial will be conducted on an outpatient basis. For all administrations, study intervention will be administered by site staff in the clinic and the participant will be observed for at least 60 minutes after the first three doses as well as at [redacted] Participants who prematurely stop dosing prior to Week 52 will be followed for regularly scheduled visits through Week 52 unless participants withdraw consent of trial participation (See Section 7.1.3) or are lost to follow-up (See Section 7.2). Participants should be followed to assess AE/SAEs for at least 12 weeks after the last study intervention administration, approximately 4, 8, and 12 weeks after the last study intervention dose, unless the participant withdraws consent. Participants who prematurely stop dosing after Week 52 but remain in the study will complete the End-of-Treatment (EOT) Visit and the SFU Period, unless the participant withdraws consent. Participants will not automatically be removed from the trial if any administration of study intervention is missed.

Rescue therapy for worsening LN may be administered at the discretion of Investigators as clinically indicated. Rescue therapy includes the initiation of any new treatment for lupus or lupus nephritis or an increase from baseline in the standard-of-care background therapy (MMF/MPA, or corticosteroids). For any rescue medications, study intervention may be continued after discussion with and approval by the Horizon Medical Monitor. However, if the participant receives a prohibited medication as a rescue, study intervention will be discontinued (See Section 6.7.2). Participants who receive rescue therapy will be considered treatment failures for subsequent endpoint analyses (such as CRR).

The primary assessment of the efficacy endpoints will be performed at [redacted]. The

final evaluation of the double-blind Treatment Period will occur at [redacted]. The SFU Period will begin after completion of the [redacted] EOT Visit and will last for 8 weeks. All participants will continue to receive SOC immunosuppressive background therapy with MMF/MPA and OCS, unless the participant has successfully discontinued OCS. Participants will continue to follow all trial requirements and will return to the clinical site for the Week 112 End-of-Study Visit for final safety assessments, as described in the Schedule of Activities (SoA), and return all remaining trial-related supplies not previously returned.

Safety assessments, including monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, and monitoring of hematology and blood chemistry, will be performed.

4.2. Scientific Rationale for Study Design

The proposed trial design is considered appropriate for assessing the efficacy, safety, tolerability, PK, and immunogenicity of daxdilimab in participants with active, proliferative lupus nephritis.

4.3. Justification for Dose

Daxdilimab has been tested in a first-in-human single-ascending dose trial in adult subjects with type I IFN-mediated autoimmune diseases, and a phase 1 multiple-ascending dose (MAD) trial in adult participants with autoimmune disease with up to [redacted]. Daxdilimab treatment resulted in rapid and durable depletion of blood pDCs. In the MAD trial, the median percent change from Baseline in CLASI-A was -dose responsive for subjects administered [redacted] Both SAD and MAD trials demonstrated acceptable safety profiles. A Phase 2 trial (Study VIB7734.P2.S1) currently enrolling participants with SLE is dosing daxdilimab at [redacted] followed by an open-label extension study (HZNP-DAX-204) to evaluate long-term safety and tolerability of daxdilimab up to Week 96.

In this Phase 2 trial in participants with active, proliferative LN, daxdilimab will be compared to placebo in addition to SOC background therapy. In a Phase 2 study in a similar population of proliferative LN patients evaluating anifrolumab up to [redacted], a Type-1 IFNAR antagonist mAb, the dosage approved for the treatment of moderate to severe SLE [redacted] was no different from placebo in inducing renal responses whereas an intensified dosing regimen consisting of 3 months of induction with anifrolumab [redacted] demonstrated a trend towards a higher proportion of patients achieving renal response at 1 year. This difference may be explained by potential IFN overexpression in the kidneys and potential loss of anifrolumab concentration due to proteinuria. One of the main mechanism of actions of pDC depletion is through suppression of the overactivated Type-1 IFN system and prompt suppression of IFN activity in the kidney is thought to be key to achieving meaningful therapeutic responses. Given the overlapping mechanism of action and potential urinary loss of daxdilimab in patients with proteinuria, we propose to initiate treatment with daxdilimab [redacted] SC or placebo at baseline, [redacted] to minimize the risk of undertreatment due to an insufficient dose or urinary loss of daxdilimab. Starting at Week 8, participants on daxdilimab will receive either daxdilimab [redacted] or daxdilimab [redacted] through [redacted]; at [redacted] all participants will be assigned to a [redacted] based upon the renal response observed at [redacted] and will either receive daxdilimab or placebo every [redacted] through [redacted] (last dose administered at [redacted]) in addition to SOC therapy.

A 52-week treatment duration is considered sufficient to demonstrate an effect on the primary and secondary outcome measures selected for this study. The second year of the trial will provide additional data to evaluate long-term safety as well as the [redacted] Current nonclinical safety data, the clinical study currently enrolling participants with SLE that will dose daxdilimab for [redacted], and belimumab's Phase 3 trial dosing through [redacted] support this treatment duration.

4.4. End-of-Study Definition

A participant is considered to have completed the trial if he or she was followed through the last protocol-specified visit (ie, Week 112), regardless of the number of doses of study intervention that were received as shown in the SoA (See Section 1.3).

The end of study date is defined as the date when the last participant across all sites is assessed (ie, last subject last visit), including any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable.

5. STUDY POPULATION

5.1. Inclusion Criteria

All participants must meet/provide all of the following criteria to be eligible for trial participation:

1. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] in the United States) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.
3. Adult men or women ≥ 18 and ≤ 80 years of age.
4. Fulfill the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for SLE (Aringer et al, 2019).
5. Have at least one of the following at Screening per central lab:
    - Antinuclear antibodies (ANA) ≥ 1:80.
    - Anti-dsDNA antibodies elevated to above normal range as established by the central laboratory (ie, positive results).
    - Anti-Smith antibodies elevated to above normal (ie, positive results).
6. Diagnosis of proliferative LN based on a renal biopsy obtained within 6 months prior to signing the informed consent form (ICF) or during the Screening Period:
    - Class III (± class V) or class IV (± class V) LN according to the World Health Organization (WHO) or 2003 ISN/RPS classification (based on local evaluation of renal biopsy).
    - Note: the local biopsy report will be used to confirm participant eligibility. The submission of Screening biopsy sample (archived or fresh tissue block, slides, or digital pathology images) for adjudication is required to participate in the study.
7. Urine protein to creatinine ratio ≥1.5 mg/mg (113.17 mg/mmol), obtained via a 24-hour urine collection at both:
    - The start of Screening and
    - Within 14 days of expected date of Randomization. Without the results of the second sample, which will be used for stratification, participants cannot be randomized. The second sample may be collected after a minimum of 10 days after the Screening sample was obtained. The second sample may be repeated once, upon approval by the Medical Monitor (this will not be considered a re-screen). Typical turn-around time for results from central laboratory is up to 7 days. On rare occasion, an extension of the 28-day screening window is allowed

if re-collection of the sample is necessary or the results needed for Randomization are delayed.

8. Estimated glomerular filtration rate (as calculated by the MDRD formula, with screening laboratory results for serum creatinine value) ≥35 mL/min/1.73 m^2.
9. Negative serum β human chorionic gonadotropin (β-hCG) test at Screening (females of childbearing potential only).
    - Note: if the result of the serum β-hCG test is borderline or thought to be false positive, the test may be repeated during the Screening Period. The participant may continue if the repeat test is negative. Women of childbearing potential (WOCBP) (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have negative serum and urine pregnancy tests during Screening and Randomization, respectively. Women of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral salpingectomy, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause and a follicle-stimulating hormone [FSH] within the postmenopausal range as established by the central laboratory during the Screening Period, unless on postmenopausal hormone replacement therapy
    - WOCBP who are sexually active with a non-sterilized male partner must agree to use a highly effective method of contraception (Table 7) from signing of the informed consent and must agree to continue using such precautions through the end of the study follow-up or 6 months (approximately 5 half-lives) following the last dose of IP in the case of early withdrawal from the study, and refrain from egg retrieval/egg donation during this period. A decision about contraception after this point should be made by the participant and her regular healthcare providers.
    - Sustained abstinence is an acceptable practice; however periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Table 7 Highly Effective Methods of Contraception

Physical Methods	**Hormonal Methods** [a]
• Intrauterine device • Intrauterine hormone-releasing system [b] • Bilateral tubal occlusion • Vasectomized partner [c] • Sexual abstinence [d]	Combined (estrogen and progestogen-containing hormonal contraception) • PO (combined pill) • Injectable • Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [e] • Injectable • Implantable • Intravaginal

	NOTE: because mycophenolate affects the metabolism of hormonal contraceptives and may reduce their effectiveness in women receiving MMF or MPA who are using hormonal contraceptives for birth control, the participant must employ an additional contraceptive method (eg, barrier method).

PO: oral(ly).

[a] Any change in hormonal birth control during the study requires use of at least two methods of highly effective contraception for at least two months.

[b] This is also considered to be a hormonal method.

[c] A vasectomized partner is a highly effective method of birth control provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] Sexual abstinence is considered to be a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant.

[e] Progestogen-only hormonal contraception where inhibition of ovulation is not the primary mode of action (minipill) is not accepted as a highly effective method.

10. Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the trial and continuing for at least 3 months (approximately 5 half-lives) after receipt of the last dose of daxdilimab and refrain from donating sperm during this period.

5.2. Exclusion Criteria

Participants will be ineligible for trial participation if they meet **any** of the following criteria at the Screening and/or Day 1 Visits, as applicable:

General Exclusion Criteria

1. Individuals involved in the conduct of the study, their employees, or immediate family members of such individuals.
2. Any condition that, in the opinion of the Investigator or the Sponsor/Central Review Committee, would interfere with evaluation of the IP or interpretation of participant safety or study results.
3. Weight > 160 kg (352 pounds) at Screening.
4. History of allergy, hypersensitivity reaction, or anaphylaxis to any component of the IP or to a previous mAb or human Ig therapy.
5. Known intolerance to ≤1.0 gm/day of MMF or equivalent dose of MPA.
6. Participation in another clinical study with an investigational drug within 4 weeks prior to Day 1 or within 5 published half-lives, whichever is longer.
7. Breastfeeding or pregnant women or women who intend to become pregnant anytime from signing the ICF through 6 months after receiving the last dose of IP.
8. History of drug or alcohol abuse that, in the opinion of the Investigator, might affect participant safety or compliance with visits, or interfere with other study assessments.

9. Major surgery within 8 weeks prior to Screening or elective surgery planned from Screening through the end of the trial.
10. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to Screening through Randomization.
11. A diagnosis of pure Class V membranous LN based on a renal biopsy obtained within 6 months prior to signing ICF or during the Screening Period.
12. History of dialysis within 12 months prior to signing the ICF or expected need for renal replacement therapy (dialysis or renal transplant) within a 12-month period after enrollment.
13. History of, or current renal diseases (other than LN) that in the opinion of the Investigator could interfere with the LN assessment and confound the disease activity assessment (eg, diabetic nephropathy).
14. Known history of a primary immunodeficiency or an underlying condition such as known human immunodeficiency virus (HIV) infection, a positive result for HIV infection per central laboratory, splenectomy, or any underlying condition that in the opinion of the Investigator significantly predisposes the participant to infection.
15. During Screening, any of the following per central laboratory (tests may be repeated once within the same Screening Period to confirm results prior to Randomization):
    - Aspartate aminotransferase > 2.5× upper limit of normal (ULN)
    - Alanine aminotransferase > 2.5× ULN
    - Total bilirubin > 1.5× ULN (unless due to Gilbert's syndrome)
    - Serum IgG < 600 mg/dL (or < 6 g/L) or < 400 mg/dL (<4 g/L) if due to active SLE/LN
    - Neutrophil count < 1000/μL (or < 1.0×10^9/L) or < 500/μL (< 0.5×10^9/L) if due to active SLE
    - Platelet count < 50,000/μL (or < 50×10^9/L) or < 25,000/μL (< 25×10^9/L) if due to active SLE
    - Hemoglobin < 8 g/dL (or < 80 g/L) or < 7 g/dL (< 70 g/L) if due to active SLE
    - Glycosylated hemoglobin > 8% (or > 0.08)
    - Total lymphocyte count < 200 cells/mm^3
16. Confirmed positive test for hepatitis B serology defined as:
    - Hepatitis B surface antigen, or
    - Hepatitis B core antibody (HBcAb) and hepatitis B virus (HBV) DNA detected above the lower limit of quantitation (LLOQ) by reflex testing by the central laboratory at Screening.

    Note that participants who are HBcAb positive at Screening will be tested every 3 months for HBV DNA. IP will be discontinued if the participant's HBV DNA levels are confirmed to exceed the LLOQ as per the central laboratory.
17. Positive test for hepatitis C virus antibody unless documented as having had successful treatment of active hepatitis C infection.
18. Active tuberculosis (TB), or a positive IFN-gamma release assay (IGRA) test at Screening, unless documented history of appropriate treatment for active or latent TB. Note that participants with an indeterminate IGRA test result with well-documented

previous treatment do not need to repeat testing and are eligible for randomization. Participants with an indeterminate IGRA test result can repeat the test, but if the repeat test is also indeterminate, they are excluded.

19. Any severe herpes virus family infection (including Epstein-Barr virus, cytomegalovirus [CMV]) at any time prior to Randomization, including, but not limited to, disseminated herpes, herpes encephalitis, recent recurrent herpes zoster (defined as 2 episodes within the last 2 years), or ophthalmic herpes.
20. Any herpes zoster, CMV, or Epstein-Barr virus infection that was not completely resolved 12 weeks prior to Randomization.
21. Any of the following within 30 days prior to signing the ICF and through Randomization:
    - Clinically significant active infection in the opinion of the Investigator, including ongoing, and chronic infection requiring antibiotics or antiviral medication (chronic nail infections are allowed).
    - Any infection requiring hospitalization or treatment with intravenous anti-infectives.
    - A participant with a documented positive SARS-CoV-2 test may be rescreened:
        - At least 2 weeks after a positive test if the participant is asymptomatic (no negative test result is required).
        - At least 3 weeks after symptomatic COVID-19 illness (no negative test result is required).
22. Opportunistic infection requiring hospitalization or parenteral antimicrobial treatment within 2 years prior to Randomization.
23. Any acute illness or evidence of clinically significant active infection on Day 1.
24. Clinically significant cardiac disease including unstable angina, myocardial infarction, congestive heart failure within 6 months prior to Randomization. Any cardiac condition including, but not limited to the following, if in the opinion of the Investigator or Medical Monitor, would increase the risk of study participation:
    - Inadequately controlled arrythmia
    - Uncontrolled hypertension
    - Presence of clinically significant abnormality on ECG
25. History of cancer within the past 5 years, except as follows:
    - In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to Screening, or
    - Cutaneous basal cell or squamous cell carcinoma treated with curative therapy.
26. Receipt of a live vaccine within 4 weeks prior to Day 1.
27. Participant should be assessed for epidemiologic risk of COVID-19 (ie, recent exposure, high-risk housing) and for health-related risk of COVID-19 severity based on current understanding of risk factors for severe disease when making a decision regarding the individual's risk of participation. Participants who have COVID-19 or other significant infection, or in the judgment of the Investigator, may be at a high risk of COVID-19 or its complications, should not be randomized.

Disease-Related Criteria

28. Active severe or unstable neuropsychiatric SLE including, but not limited to: aseptic meningitis, cerebral vasculitis, myelopathy, demyelination syndromes (ascending,

transverse, acute inflammatory demyelinating polyradiculopathy), acute confusional state, impaired level of consciousness, psychosis, acute stroke or stroke syndrome, cranial neuropathy, status epilepticus, cerebellar ataxia, and mononeuritis multiplex:

a) That might cause the participant to be unable to fully understand the ICF.

OR

b) In the opinion of the Investigator, protocol-specified SOC is insufficient to control neurologic features of SLE and utilization of a more aggressive therapeutic approach, such as adding IV cyclophosphamide and/or high dose IV pulse corticosteroid therapy or other treatments not permitted in the protocol, is indicated or anticipated.

29. Documented history of systemic sclerosis or diagnosis of SLE with overlapping systemic sclerosis.
30. History of, or current diagnosis of, catastrophic anti-phospholipid syndrome (APS) or APS-related thromboembolic event or pregnancy loss within 1 year prior to signing the ICF. Participants with APS adequately controlled by anticoagulants or aspirin for at least 12 weeks may be recruited to the study.
31. History of any non-SLE disease that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to signing the ICF.

Prior and Concomitant Therapy Criteria

32. Receipt of any of the following treatments within the following timeframes.
    - 6 weeks prior to Randomization:
        - Opioid use above 40 mg/day morphine-equivalent, unstable dosing, or initiation of regular dosing
        - IV corticosteroids > 3.0 gm (cumulative dose)
    - 8 weeks prior to Randomization:
        - Immunoglobulins (except anti-SARS-CoV-2 therapeutic antibodies)
        - Calcineurin inhibitors (eg, cyclosporin, voclosporin, tacrolimus), mechanistic target of rapamycin inhibitors, retinoids, thalidomide, lenalidomide, or Janus kinase inhibitors
        - Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis, plasma exchange, or Therakos® photopheresis
    - 12 weeks (or 5 half-lives, whichever is longer) prior to Randomization:
        - IV cyclophosphamide > 2 pulses of high dose ($\geq$ 0.5 gm/m^2) or > 4 doses of low-dose (500 mg every 2 weeks)
        - Alkylating agents other than cyclophosphamide (eg, chlorambucil)
        - Cytokine or cytokine receptor antagonists, including but not limited to interleukin (IL)-1, IL-6, IL 17, IL-12/23, IL-23, IFN, integrin, or TNFα antagonists (except for IFNα kinoid, for which receipt at any time is exclusionary)
        - Belimumab, abatacept, or eculizumab

  - Other biologics used for immunosuppression or immunomodulation (eg, IFN therapy, IL-2)
  - Investigational drugs
  - IPP-201101 (Lupuzor™)
- 24 weeks prior to Randomization:
  - B cell-depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, inebilizumab, telitacicept) other than atacicept or obinutuzumab
  - Receipt of systemic glucocorticoids (ie, PO, rectal, IV or IM) for more than a total of 2 weeks for any concurrent illness, including asthma, inflammatory bowel disease, or drug-induced SLE
- 40 weeks prior to Randomization:
  - Atacicept
- 1 year prior to Randomization:
  - Bacille-Calmette-Guerin (BCG) vaccination
- 1.5 years prior to Randomization:
  - Obinutuzumab
- The following medications must be discontinued prior to the day of Randomization (because of potential interaction with MMF):
  - Methotrexate
  - Azathioprine
  - Leflunomide
  - Mizoribine
  - Proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole, etc.)
  - Cholestyramine

5.3. Restrictions

5.3.1. Fasting Lipid Profile

Participants will be required to fast for at least 8 hours prior to assessment of lipid profile at the visits described in the SoA (See Section 1.3). If the participant has not fasted, he/she should fast before the next visit, and the test can be done at that visit.

5.3.2. Perioperative Management of Investigational Product

Planned surgeries should be avoided during the study if clinically feasible.

5.3.3. Major Surgeries

Pre-operative management of study intervention: If a non-urgent major surgery becomes necessary during the study, it should be scheduled at least 4 weeks after the last administration of study intervention, if clinically feasible. The determination of whether or not a surgery is "urgent" will be at the discretion of the Investigator, preferably in consultation with the Sponsor/Designee Medical Monitor.

5.3.4. Non-Major Surgeries

The decision to withhold study intervention administration is at the Investigator's discretion.

Post-operative management of study intervention: study intervention administration may be resumed at the Investigator's discretion after all of the following criteria are met:

External wound healing is complete and
Any post-operative antibiotic course is completed and
All acute surgical complications have resolved.

5.3.5. Blood Donation

Participants must not donate blood from date of Randomization until 6 weeks after the last dose of MMF/MPA.

5.4. Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but are not subsequently enrolled in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this trial ("Screen Failure") may be rescreened once, if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that the participant can satisfy all of the eligibility criteria. All procedures planned at the Screening Visit, including signature of a new informed consent form, will be performed. Additional information regarding rescreening will be provided in the Interactive Response Technology (IRT) Manual.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

This trial involves SC administration of daxdilimab [redacted] or [redacted] mg or placebo [redacted] based upon the renal response observed at [redacted] of either daxdilimab [redacted] or [redacted] mg or placebo [redacted] (See Table 5 and Table 6). The study intervention (IP and placebo) will be administered by trial site staff in the clinic. On [redacted], participants will remain under observation for at least 1 hour after administration of study intervention. In addition, The IP will be provided by the Sponsor. Further details regarding the IP and placebo can be found in Table 8.

Table 8 Study Interventions Administered

Intervention Label	**Investigational Product**	**Placebo**
Intervention Name	Daxdilimab	Placebo
Intervention Description	[redacted]	Normal Saline
Type	Active Drug	Placebo
Dose Formulation	2R vial	See Pharmacy Manual.
Dosage Level(s)	[redacted]	
Route of Administration	SC injection	SC injection
Sourcing	Horizon Therapeutics	Commercially available normal saline
Packaging and Labeling	Please refer to the study-specific Pharmacy Manual for information on packaging and labeling. The label text for the study interventions will comply with applicable regional, national, and local laws and regulations and will include at a minimum the protocol number, contents of the vial, the appropriate regional cautionary statements, lot number, storage conditions, and the name of the Sponsor.	
Administration Instructions	Daxdilimab should be administered by clinic staff trained in best practices for SC administration of treatments. More details on the administration method are described in the Pharmacy Manual.	Placebo should be administered by clinic staff trained in best practices for SC administration of treatments. More details on the administration method are described in the Pharmacy Manual.

2R = 2 mL injection vial; HCl = hydrochloric acid; [redacted]; SC = subcutaneous.

The contents of the label will be in accordance with all applicable regulatory requirements.

In addition to study intervention, participants will be expected to adhere to SOC immunosuppressive background therapy, consisting of the combination of MMF/MPA and corticosteroids. Participants may enter the study taking daily OCS at a maximum dose of 0.5 mg/kg/day of prednisone-equivalent, not to exceed 40 mg/day, and must be on a stable dose for at least 10 days prior to Randomization. In addition, participants will receive IV methylprednisolone pulse 500 mg on the day of Randomization, prior to receiving the study intervention, unless they received a methylprednisolone pulse of ≥ 500 mg within 10 days prior to Randomization followed by a reducing taper of OCS for participants already taking OCS prior to entry. For participants who are not already taking prescribed MMF prior to Randomization, the dosing of MMF will start at 500 mg BID for a total daily dose of 1 gm/day for the first week, increasing to 1 gm BID for a total daily dose of 2 gm/day for the second and subsequent weeks (ie, beginning on Day 8). An equivalent dose of MPA may be used as an alternative to MMF. See Section 6.7.4.1 for additional details.

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Preparation and Administration

[redacted]

Placebo is to be procured as commercially available Normal Saline.

Study intervention (daxdilimab and placebo) is to be administered SC. To maintain the same number and volume of injections across all groups, the required dose will be administered by [redacted].

The first day of dosing is considered Day 1. To reduce the risk of unblinding to the study personnel who will be evaluating the participant, study intervention will be administered by an unblinded pharmacist/IP Manager or a study site staff member who is not otherwise involved in the participant's participation in the study. The study intervention administrator should be experienced in performing SC injections. The skin surface of the anterolateral thigh, upper outer triceps area, upper buttocks, or abdomen (avoiding a 2-inch [5 cm] radius around the umbilicus) should be prepared with an alcohol wipe and allowed to air dry. The skin will be pinched to isolate SC tissue from the muscle. The needle will be inserted at a 90-degree angle to the skin surface approximately halfway into the SC tissue. The prepared study intervention will be slowly injected (at least 5 second duration is recommended per [redacted] syringe) into the SC tissue using gentle pressure. The area should not be massaged after injection. The SC injection site can be changed during the study as per the participant's preference.

Further guidance and information for the preparation and administration of study intervention are provided in the Pharmacy Manual.

6.2.2. Labeling

Trial drug packaging will be in compliance with Sponsor standard procedures and will meet all local requirements.

6.2.3. Storage

Daxdilimab vials must be refrigerated at 2-8°C (36°F to 46°F) until the day of use.

IP will be dispensed by the trial site only for administration to trial participants.

6.2.4. Drug Accountability

The Principal Investigator at each site is responsible for the control of all trial drugs and delegating preparation and drug accountability responsibilities to a pharmacist (or designee in accordance with institutional policies and local regulations), who must maintain adequate records of the receipt and disposition of all trial drugs shipped to the site. Records will include receipt dates, condition at time of receipt, quantities received, quantities dispensed, quantities returned or destroyed and the identification numbers of the participant who received trial drug.

As permitted by site policy, all empty, partially empty, and full vials of trial drug must be retained by the site under locked storage until drug accountability has been completed. Periodically throughout the trial and at the conclusion of the trial, inventory checks and accountability of trial materials will be conducted by a representative of the Sponsor. Once accountability is completed, the Sponsor's representative will either authorize onsite destruction or the return of trial drug (all used, partially used and unused vials) to Almac Clinical Services, or contracted depots, for central destruction.

The completed Drug Accountability and Drug Return/Destruction Record(s) will be returned to the Sponsor's representative. The Investigator's copy of the Drug Accountability and Drug Return/Destruction Record(s) must document accurately the return and/or destruction of all trial drug and be maintained by the pharmacist or designee.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

An interactive voice/web response system (IXRS) will be used for Randomization on Day 1 to a Treatment Group (daxdilimab [redacted] mg, [redacted] mg, or placebo) and assignment of study intervention kit numbers. A participant is considered randomized into the study when the Investigator or appropriate designee notifies the IXRS that the participant meets eligibility criteria and the IXRS provides the assignment of treatment group.

[redacted] (See Section 4.1). After the Investigator or appropriate designee notifies the IXRS of the participants' observed renal responses from the [redacted] the IXRS provides the assignment of study intervention kit numbers.

Additional details are provided in the IRT Manual.

The Randomization dates are to be documented in the participant's medical record and on the enrollment case report form (CRF).

6.4. Blinding/Masking

This is a double-blind trial; therefore, the Sponsor, Investigator and participants will not know the treatment administered.

To reduce the risk of unblinding to the trial personnel who will be evaluating the participant, an otherwise uninvolved, unblinded third party (eg, a pharmacist/IP Manager or trial-site staff member) will be responsible for the dispensation and administration of all trial interventions and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

This third party will instruct the participant to avoid discussing the dosing or packaging of the trial intervention with the Investigator.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded trial intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately.

In the event of unblinding, the instructions in the IRT Manual will apply.

6.5. Treatment Compliance

When participants are dosed at the site, they will receive study intervention directly from the pharmacist/IP Manager, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The Principal Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

An inventory of the trial drug supplies will be performed by the authorized site designee and recorded onto the Drug Accountability Log in the participant's source document records or equivalent.

A record of the quantity of daxdilimab or placebo dispensed and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.6. Treatment of Overdose

In the event of an overdose, the Investigator/treating physician should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Consultation with the Medical Monitor is required for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with

the Medical Monitor is also required even if there are no adverse events, in order to discuss further management of the participant. If the overdose results in clinically apparent or symptomatic adverse events, the participant should be followed carefully until all signs of toxicity are resolved or returned to baseline and the AE(s) should be recorded/reported.

6.7. Prior and Concomitant Therapy

6.7.1. Concomitant Medications

Participants must be instructed not to take any medications, including over-the-counter (OTC) products, without first consulting the Investigator.

Concomitant (including immunosuppressant) medications should be administered consistently and if possible after all visit procedures and assessments, including study intervention administration and post-administration PK blood draws (if applicable).

Participants who are taking concomitant medications must be informed that on the day of the study visit, these medications are to be taken only after the study procedures and assessments are completed (if clinically appropriate) or as advised by the Investigator.

At each visit, use of any rescue therapy for worsening LN and restricted or prohibited medication beyond the protocol allowed threshold will also be assessed.

6.7.2. Prohibited Medications

Receipt of any of the following treatments leads to immediate discontinuation of study intervention:

- IV, intramuscular, or SC immunoglobulins, except anti-SARS-CoV-2 therapeutic antibodies
- Cyclophosphamide or alkylating agents (eg, chlorambucil)
- Calcineurin inhibitors (eg, cyclosporin, voclosporin, tacrolimus), mechanistic target of rapamycin inhibitors, retinoids, thalidomide, lenalidomide, or Janus kinase inhibitors.
- Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis, plasma exchange, or Therakos® photopheresis.
- Live vaccines (the Sponsor recommends that Investigators ensure all participants are current with recommended vaccinations per local treatment standards prior to entry into the study).
- Cytokine or cytokine receptor antagonists, including but not limited to interleukin (IL)-1, IL-6, IL 17, IL-12/23, IL-23, IFN, integrin, or TNFα antagonists (except for IFNα kinoid, for which receipt at any time is exclusionary).
- Belimumab, abatacept, or eculizumab
- Other biologics used for immunosuppression or immunomodulation (eg, IFN therapy, IL-2)

- Investigational drugs
- IPP-201101 (Lupuzor™)
- B cell-depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, inebilizumab, telitacicept) other than atacicept or obinutuzumab
- Receipt of systemic glucocorticoids (ie, PO, rectal, IV or IM) for more than a total of 2 weeks for any concurrent illness, including asthma, inflammatory bowel disease, or drug-induced SLE
- Atacicept
- BCG vaccination
- Obinutuzumab

6.7.3. Restricted Medications

As daxdilimab is an investigative immunomodulatory agent, non-protocol permitted changes to immune modifiers or immunosuppressants during the study are not allowed. If a participant receives one of the following after Randomization, the Investigator must notify the Sponsor/Designee Medical Monitor immediately. The Designee Medical Monitor will determine with the Sponsor if the participant may continue to receive study intervention; however, the participant would be considered a non-responder for efficacy assessments such as CRR.

- Azathioprine
- Methotrexate
- Leflunomide
- Mizoribine
- Cholestyramine
- Increase in corticosteroids (except methylprednisolone pulses) above the protocol allowed doses or duration
- Corticosteroids with a long biologic half-life (ie, dexamethasone, betamethasone)
- MMF/MPA dose above or below protocol required dose or duration

6.7.4. Permitted Therapies

6.7.4.1. Standard of Care Immunosuppressive Background Therapy

Permitted medications for SOC treatment for LN are described below. The SOC for LN will consist of the combination of MMF/MPA and corticosteroids.

6.7.4.1.1. Mycophenolate Mofetil/Mycophenolic Acid

The target dose of MMF will be 2 gm/day by mouth (or equivalent) throughout the study, where the dose is titrated to the target dose between Randomization and Week 8. For participants who are not already taking prescribed MMF prior to Randomization, the dosing of MMF will start at 500 mg BID for a total daily dose of 1 gm/day for the first week, increasing to 1 gm BID for a total daily dose of 2 gm/day for the second and subsequent weeks (ie, beginning on Day 8). An equivalent dose of MPA may be used as an alternative to MMF. All participants will take

MMF/MPA BID (ie, morning and evening), before meals (ie, on an empty stomach), with a glass of water. If a dose is missed, the participant should take the next correct dose rather than "doubling up" at the next dosing time point. A stable dose of MMF/MPA should be maintained throughout the study. Adjustments of the dose due to suboptimal response, toxicity, or intolerability are allowed if needed according to guidelines described below. A maximum dose of 3.0 gm/day is allowed up to Week 24 for participants with suboptimal response between Weeks 8 and 24 with a reduction to ≤ 2.0 gm/day by Week 32. The dose of MMF must be stable from Week 40 to Week 52.

After Week 52, MMF dose should be ≤2 gm/day. If MMF dose >2 gm/day at Week 52, taper to ≤2 gm/day is recommended by Week 60. The dose of MMF must be stable from Week 92 to [redacted].

It is not mandatory for a participant to receive 2 gm/day of MMF (or equivalent) if local treatment standards dictate a lower dose to be given (eg, for constitutionally small participants). The minimum dose of MMF is 1.0 gm/day (or equivalent) after Week 8 through [redacted]. Participants who do not tolerate the minimum MMF dose (or equivalent) will be considered non-responders for responder analyses (such as CRR) but will be allowed to continue to receive study intervention. However, if MMF/MPA is discontinued and a different immunosuppressant is started, the study intervention will be discontinued. A decrease below the minimum dose or withholding MMF/MPA for 14 days or less for MMF/MPA related side effects, such as gastrointestinal side effects, cytopenias or infection is acceptable at any time throughout the study. If MMF/MPA must be withheld or decreased below the minimum dose for more than 14 days, the participant will be considered a non-responder for responder analyses (such as CRR) but may continue to receive study intervention (this will not be considered as non-compliance or a protocol deviation because the withdrawal of MMF/MPA is for safety reasons).

The use of IV forms of mycophenolate is prohibited.

Initial adjustment of MMF/MPA dose to achieve or maintain the target dose (Randomization through Week 8)

- Participants who are receiving MMF/MPA at a dose of 2 gm/day (or equivalent) at Week 0 (Day 1) will continue this dose without interruption.
- Participants who are not taking MMF/MPA at Week 0 (Day 1) or participants who are taking less than 2 gm/day (or equivalent), the dose will be titrated up with the goal of achieving a dose of 2 gm/day (or the therapeutic target dose if local treatment standards dictate a lower dose) by Week 1 (Day 8) (but not later than Week 8 (Day 57), if dose escalation is limited by intolerability).

  Titration of MMF/MPA should follow accepted local practice guidelines, including appropriate laboratory monitoring for toxicity.
- Participants who at Week 0 (Day 1) are taking MMF doses > 2 gm/day will have their dose reduced to 2 gm/day by Week 8 (Day 57) unless they meet criteria for suboptimal response (see below for suboptimal response).

MMF/MPA dose between Week 8 and 24

The dose of MMF/MPA will be kept stable from Week 8 through Week 24 unless dose escalation to a maximum of 3 gm/day is necessary for suboptimal response (defined below) or a dose reduction is necessary to manage toxicity or intolerability.

Criteria for suboptimal response:

A suboptimal response is defined by UPCR values shown below **at two** independent measurements taken at least 2 weeks apart:

- Spot UPCR> 3 mg/mg and
- Spot UPCR< 15% decrease compared to baseline spot UPCR

If a participant meets the criteria at or after Week 8, the dose may be escalated or kept above 2 gm/day. After initial confirmation of suboptimal response, MMF/MPA can be increased up to 3 gm/day (or equivalent) until Week 16 without re-testing for the suboptimal response criteria. The dose of MMF/MPA must be kept stable from Week 16 unless dose reduction is necessary for intolerability or MMF/MPA-related AEs. A temporary decrease below the minimum dose or withholding MMF/MPA for 14 days or less for MMF related side effects, such as gastrointestinal side effects, for cytopenias or infection is acceptable.

MMF/MPA dose between Week 24 and Week 52:

For participants who are taking > 2 gm/day of MMF (or MPA equivalent) at Week 24, the dose of MMF/MPA must be decreased to a maximum dose of 2 gm/day (or equivalent) by Week 32. **The dose of MMF/MPA must be stable from Week 40 through Week 52 (unless a dose reduction is necessary to manage toxicity or intolerability)**.

MMF/MPA dose from Week 52 to [redacted]

The target dose of MMF/MPA will be ≤2 gm/day. If the MMF/MPA dose is >2 gm/day at Week 52, it should be tapered to ≤2 gm/day by Week 60.

MMF/MPA dose must not be changed from Week 92 to [redacted].

6.7.4.1.2. Corticosteroids

Initial corticosteroid treatment to control LN and SLE:

Participants may enter the study taking daily OCS at a maximum dose of 0.5 mg/kg/day of prednisone-equivalent, not to exceed 40 mg/day, and must be on a stable dose for at least 10 days prior to Randomization. In addition, participants will receive IV methylprednisolone pulse 500 mg on the day of Randomization, prior to receiving the study intervention, unless they received a methylprednisolone pulse of ≥ 500 mg within 10 days prior to Randomization. Participants may also receive one additional (optional) dose of IV methylprednisolone pulse (≤ 500 mg) for renal or extra-renal disease activity after the Week 0 (Day 1) Visit up to and including the Week 8 Visit. Methylprednisolone pulse can be divided and administered on two consecutive days, but the cumulative dose must not exceed 500 mg.

Steroid tapering during the study

Oral corticosteroid dose tapering is required during the study with the goal of fractionally reduce OCS to a prednisone-equivalent dose of ≤ 7.5 mg/day by Week 12 and prednisone-equivalent dose of ≤ 2.5 mg/day by Week 24. The rate of tapering is at the discretion of the Investigator; a recommended tapering schedule is provided below.

Table 9 Recommended Oral Prednisone Tapering Schedule

Starting Prednisone Dose (mg/day)	10 mg/day	20 mg/day	30 mg/day	40 mg/day
Week 2 (Day 15)	10	15	25	35
Week 4 (Day 29)	10	15	25	30
Week 6 (Day 43)	7.5	10	20	25
Week 8 (Day 57)	7.5	10	15	20
Week 10 (Day 71)	5	7.5	10	15
Week 12 (Day 85)	5	7.5	7.5	7.5
Week 16 (Day 113)	2.5	5	5	5
Week 20 (Day 141)	2.5	2.5	2.5	2.5
Week 24 (Day 169)	2.5	2.5	2.5	2.5

If participants experience an increase in SLE disease activity upon tapering of OCS, their dose may be returned to a dose equal to or less than the dose prior to the taper. The return to the pre-taper dose will not be considered an OCS "burst and taper". The pre-taper dose for various periods is defined as follows:

- Week 0 to Week 12: dose at Randomization
- After Week 12 to Week 24: the Week 12 dose
- After Week 24 to Week 44: the Week 24 dose

Participants unable to taper OCS to ≤ 15 mg/day at Week 12 or ≤ 10 mg/day at Week 24 will be discontinued from study intervention treatment (See Section 7.1.1). However, participants who exceed the maximum daily OCS dose at the Week 12 or Week 24 Visits may continue to receive study intervention if the current dose is part of a protocol allowed temporary OCS dose (eg, burst and taper) increase. Participants who cannot be returned to their pre-increase dose within 14 days from the start of burst will have their study intervention discontinued at the next visit.

Participants who prematurely stop dosing prior to Week 52 will be followed for regularly scheduled visits through Week 52 unless participants withdraw consent of trial participation (See Section 7.1.3) or are lost to follow-up (See Section 7.2). Participants should be followed to assess AE/SAEs for at least 12 weeks after the last study intervention administration, approximately 4, 8, and 12 weeks after the last study intervention dose, unless the participant withdraws consent.

Participants who prematurely stop dosing after Week 52 but remain in the study will complete the EOT Visit and the SFU Period, unless the participant withdraws consent. Participants will not automatically be removed from the trial if any administration of study intervention is missed

Investigators will not be required, but may continue, to taper OCS dose beyond the target of 2.5 mg/day up to Week 40, including discontinuation of OCS. **Steroid tapering will not be permitted from Week 40 to Week 52**.

Continued tapering of OCS is recommended for all participants after the Week 52 Visit with the goal of achieving discontinuation (ie, 0 mg) by Week 76. Due to variability in participant responses to OCS treatment and tolerability of taper, Investigators will have flexibility of when the OCS dose is reduced at each visit. No change in OCS dose will be allowed from Week 92 to [redacted]

Steroid "burst and taper"

A steroid burst is defined as one of the following:

- OCS increase up to a maximum daily dose of 0.5 mg/kg/day (maximum 40 mg/day) prednisone-equivalent dose for up to a total of 14 days which must be fully administered and tapered to less than or equal to the pre-burst starting dose by the end of the 14th day. Any course of OCS burst must not extend beyond Week 40, regardless of when the course was started.

OR

- A maximum of 1 instance of intra-articular, tendon sheath or bursal injections (for a total dose of methylprednisolone ≤ 80 mg or equivalent) can be given. Participants who receive any intraarticular/tendon sheath/bursal injections should not receive OCS burst (and vice versa).

Steroid burst is allowed as follows**:**

- **From Randomization to Week 40:** One burst and taper of corticosteroids for increased SLE disease activity or for non-SLE activity is allowed.

  Participants who receive more than one steroid "burst and taper" or who violate the above criterion may continue to receive study intervention after approval by Sponsor/Designee Medical Monitor, but will be considered non-responders for subsequent responder analyses (such as CRR) to be further described in the SAP, regardless of whether the OCS "burst" was administered for increased SLE activity or non-SLE causes.
- **Increase in corticosteroids from Week 40 to Week 52:** No increase in OCS, or the use of IV or intra-articular, tendon sheath or bursal injections is allowed from Week 40 until the Week 52 assessment.
- One burst and taper will be allowed between Week 52 and Week 92.

Increase in corticosteroids for the prevention of adrenal insufficiency

For a severe illness, surgery, or symptoms of adrenal insufficiency, if clinically warranted, the following can be used, in addition to the "burst and taper" described above from Randomization to Week 40 without the participant being considered a non-responder:

- Oral or IV hydrocortisone up to 100 mg every 8 hours on the first day followed by half of the previous dose for 2 days before returning to their usual dose **OR**

- Participants who are taking ≤ 7.5 mg/day prednisone or equivalent will be allowed to receive up to an additional 7.5 mg/day to a total of 15 mg/day oral prednisone or equivalent for a total of up to 14 days.

Participants who receive either of these corticosteroid regimens for the prevention of adrenal insufficiency between Week 40 and Week 52 will be considered as a non-responder for the analyses at Week 52.

6.7.5. Other Concomitant Medications

Medications other than the SOC immunosuppressive background therapy described above, which are considered necessary for the participant's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the electronic Case Record Form (eCRF). Participants should not start naturopathic, herbal, ayurvedic remedies, nutritional/dietary supplements, vitamins, and/or minerals without discussing with the Investigator.

6.7.5.1. Anti-Hypertensive Agents and HMG-CoA Reductase Inhibitors (Statins)

Routine use of Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Blockers (ARB) is recommended for all participants unless contraindicated. Use of anti-proteinuric agents are allowed during the study if they had been started at least 10 days prior to the assessment of the second screening 24-hour UPCR sample (ie, the first sample for 24-hour UPCR is collected at the start of the Screening process and the second sample is collected within 14 days prior to the expected date of Randomization). The dose may be adjusted to optimize anti-hypertensive effects or to reduce ACEI/ARB-related side effects up to Week 4. The dose must be kept stable from Week 4 through [redacted]. Dose reductions are allowed only to reduce ACEI/ARB-related side effects such as hypotension, increase in creatinine, or cough. If cough develops, ACEI may be changed to ARB. Changes in other classes of anti-hypertensive agents (eg, calcium channel receptor blockers, beta-adrenergic receptor blockers, alpha-adrenergic receptor blockers) are allowed as clinically indicated to optimize blood pressure.

Statins must be kept at stable doses after Day 1. Decreases in the dose are allowed only to reduce statin-related side effects.

Cholestyramine must be discontinued prior to the day of Randomization.

6.7.5.2. Sodium-Glucose Cotransport 2 Inhibitors

Use of Sodium-Glucose Cotransport 2 (SGLT2) inhibitors is allowed during the study if they had been initiated to treat Type 2 diabetes mellitus only. No increase in the dose of or initiation of SGLT2 inhibitors should be made between signing the ICF and Randomization. For participants receiving SGLT2 inhibitors, the dose must remain stable from Randomization through [redacted] and may be reduced only for reasons of toxicity but not for efficacy.

6.7.5.3. Anti-Malarial Agents

The dose of anti-malarial agents should remain stable throughout the study except where a dose reduction is necessary to manage anti-malarial-related AEs. Any anti-malarial-related abnormality should be managed according to local standards. Discontinuation of antimalarials is

allowed, if necessary, to manage anti-malarial-related AEs. The participant may remain in the study even if anti-malarial agents are stopped.

All participants who have been taking anti-malarial therapy within 12 months of signing the ICF must have an eye exam by a qualified professional either within 12 months prior to signing the ICF or within 12 weeks after signing the ICF. Anti-malarial-related abnormalities should be managed according to local standards. Anti-malarial-related abnormalities do not exclude participants if they meet all other eligibility criteria. If an eye exam is not performed within the protocol specified timeframe, it will be considered as a protocol deviation.

6.7.5.4. Non-Steroidal Anti-inflammatory Drugs

No increase in the dose of or initiation of a new prescription non-steroidal anti-inflammatory drugs (NSAID) should be made between signing the ICF and Randomization. For participants receiving NSAIDs, concomitant histamine H2-receptor antagonists should be considered according to local practice and in concordance with considerations in the mycophenolate label.

The dose of prescription NSAIDs must remain stable from Randomization through [redacted] and may be reduced only for reasons of toxicity but not for efficacy. Prescription NSAIDs should not be administered with other NSAIDs (including OTC NSAIDs) except for low-dose aspirin (≤ 325 mg/day).

Non-prescription NSAIDs

- NSAIDs for analgesic purposes that never exceed label-approved doses of NSAIDs may be used for pain as required, based on Investigator judgement for up to 1 week at a time.
- Low-dose aspirin (maximum of 325 mg/day) for cardioprotection is permitted.

6.7.5.5. Acetaminophen (Paracetamol)

Normal release (not extended release) acetaminophen/paracetamol may be used for pain as required.

6.7.5.6. Narcotic Analgesics

Narcotic analgesics may be used during the study as clinically indicated.

6.7.5.7. Topical Therapy

Concurrent use of topical therapy for cutaneous lupus erythematosus (eg, topical corticosteroids, topical immunosuppressants) is permitted. During the study, topical therapy may be reduced or discontinued based on clinical manifestations and Investigator discretion. Should cutaneous skin manifestations reoccur, the same topical therapy may be resumed at same dose as was being used at the time of Randomization.

It is encouraged that no new dermatologic preparations be initiated for the duration of the study. Participants should use sunscreen (list as concomitant medication for SLE) and avoid sun exposure for the duration of the study.

6.7.6. Rescue Medicine

The study site will supply rescue medication at any time during the study. Although the use of rescue medications is allowable, the use of rescue medications should be delayed, if possible. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Rescue therapy for worsening LN may be administered at the discretion of Investigators as clinically indicated. Rescue therapy includes the initiation of any new treatment for lupus or LN or an increase from baseline in the SOC background therapy (MMF/MPA or corticosteroids). For any rescue medications, study intervention may be continued after discussion with and approval by the Horizon Medical Monitor. However, if the participant receives a prohibited medication as a rescue, study intervention will be discontinued. Participants who receive rescue therapy will be considered treatment failures for subsequent endpoint analyses (such as CRR).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants have the right to withdraw from the trial at any time for any reason without penalty. The Investigator also has the right to withdraw participants from treatment if he or she feels it is in the best interest of the participant or if the participant is uncooperative or noncompliant.

Should a participant decide to withdraw and does not plan to participate in the post-treatment SFU Period, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the Early Termination (ET) Visit.

The Investigator or one of his or her staff members should contact the participant to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the participant's withdrawal should be made with an explanation of why the participant is withdrawing from the trial. If the reason for withdrawal is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

If a participant withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site trial records.

7.1. Discontinuation

Any participant who decides to discontinue from the trial prematurely and does not plan to participate in the post-treatment SFU Period will be requested to complete the ET Visit.

Participants who discontinue will not be replaced.

7.1.1. Discontinuation of Study Intervention

Blinded study intervention will be discontinued in participants who meet pre-defined criteria for worsening LN or SLE.

Criteria for discontinuing study intervention for worsening LN or SLE (at any time):

- > 30% decrease in eGFR compared to baseline due to LN **and** eGFR < 60 mL/min/1.73 m^2 (compared to the average of the previous two visits, not explained by change in comorbidities or concomitant medications. A decrease in eGFR must be confirmed on at least two independent samples at least 5 days apart after non-SLE causes have been corrected or excluded) **OR**
- Increase in renal or extra-renal lupus activity requiring prohibited systemic immunosuppressive treatment (eg, cyclophosphamide, rituximab, belimumab) **OR**
- Receipt > 1 methylprednisolone pulse after the day of Randomization **OR**
- Receipt of any methylprednisolone pulse after Week 8 **OR**
- The study intervention will be discontinued if MMF is discontinued, and another immunosuppressant is initiated

Criteria for discontinuing study intervention for worsening LN or SLE at Week 12 and Week 24:

- eGFR < 75% of baseline and < 60 mL/min/1.73 m^2 (compared to the average of the previous two visits, not explained by change in comorbidities or concomitant medications. A decrease in eGFR must be confirmed on at least two independent samples at least 5 days apart after non-SLE causes have been corrected or excluded) **OR**
- Nephrotic range UPCR (confirmed by a second measurement at least two weeks after the first measurement):
    - Participants with 24-hour UPCR ≤ 3 mg/mg at baseline will be withdrawn if 24-hour UPCR increases by > 50% from baseline to > 3.5 mg/mg
    - Participants with 24-hour UPCR > 3 mg/mg at baseline will be withdrawn if 24-hour UPCR **at Week 24** > 3.5 mg/mg and there is < 50% improvement from baseline

      OR
- Inability to adhere to corticosteroids requirements:
    - Inability to reduce OCS to ≤ 15 mg/day prednisone-equivalent at Week 12
    - Inability to reduce OCS to ≤ 10 mg/day prednisone-equivalent by Week 24

Participants who exceed the maximum daily OCS dose at the Week 12 or Week 24 Visits may continue to receive study intervention if the current dose is part of a temporary increase in OCS dose (eg, protocol allowed burst and taper). Participants who cannot be returned to their pre-increase dose within 14 days from the start of the increase will have their study intervention discontinued at the next visit.

Participants who prematurely stop dosing prior to Week 52 will be followed for regularly scheduled visits through Week 52 unless participants withdraw consent of trial participation (See Section 7.1.3) or are lost to follow-up (See Section 7.2). Participants should be followed to assess AE/SAEs for at least 12 weeks after the last study intervention administration, approximately 4, 8, and 12 weeks after the last study intervention dose, unless the participant withdraws consent.

Participants who prematurely stop dosing after Week 52 but remain in the study will be complete the EOT Visit and the SFU Period, unless the participant withdraws consent. Participants will not automatically be removed from the trial if any administration of study intervention is missed.

Early discontinuation of study intervention for reasons other than lack of efficacy

An individual participant will not receive any further study intervention if any of the following occur in the participant:

- Receipt of Prohibited Medications (See Section 6.7.2).
- A Common Terminology for Adverse Events (CTCAE v5.0 dated 27 NOV 2017) Grade 3 or higher allergic reaction to the study intervention.
- A CTCAE Grade 3 or higher infection considered related to the study intervention.
- Other AE that contraindicates further dosing in the opinion of the Investigator and/or the Sponsor, or Medical Monitor.

- Withdrawal of consent from further treatment with study intervention.
- Participant is determined to have met one or more of the exclusion criteria or failed to meet all the inclusion criteria for study participation and there is a potential safety risk associated with continuation identified upon consultation with the Medical Monitor.
- Pregnancy or a decision to become pregnant.
- Any of the following liver function abnormalities:
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 8× ULN.
  - ALT or AST ≥ 5× ULN for more than 2 weeks.
  - ALT or AST ≥ 3× ULN and total bilirubin ≥ 2× ULN.
  - ALT or AST ≥ 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥ 5%).

Participants who prematurely stop dosing prior to Week 52 will be followed for regularly scheduled visits through Week 52 unless participants withdraw consent of trial participation (See Section 7.1.3) or are lost to follow-up (See Section 7.2). Participants should be followed to assess AE/SAEs for at least 12 weeks after the last study intervention administration, approximately 4, 8, and 12 weeks after the last study intervention dose, unless the participant withdraws consent.

Participants who prematurely stop dosing after Week 52 but remain in the study will be complete the EOT Visit and the SFU Period, unless the participant withdraws consent. Participants will not automatically be removed from the trial if any administration of study intervention is missed.

Site Investigators will be trained about the importance of retention of participants through the completion of the study, and participants will be informed about the continued scientific importance of their data even if they discontinue study intervention early.

7.1.2. Discontinuation from the Trial

Reasons for discontinuation from the trial include the following:

- The participant is lost to follow-up.
- The Sponsor or regulatory authorities, for any reason, stop the trial. In this case, all participants will be discontinued from the trial. The Investigator will immediately, on discontinuance of the trial by the Sponsor, in its entirety or at a clinical trial site, inform both the participants and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of participants or other persons.

7.1.3. Withdrawal of Consent from the Trial

Participants are free at any time to withdraw from the study (study intervention and assessments), without prejudice to further treatment (withdrawal of consent). Such participants will always be asked about the reason(s) for withdrawal and the presence of any AEs. If a participant withdraws participation in the study, then no further study visits or data collection should take place. Further details concerning use of samples collected during the study from a participant who withdraws consent are provided in Section 10.9.

7.2. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the trial site staff.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site will attempt to contact the participant and reschedule the missed visit. The site will then counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to or should continue in the trial.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or trial file.
- If all attempts to contact the participant fail, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Description of Study Procedures and Assessments

Trial procedures and their timepoints are summarized in the SoA (see Section 1.3). Protocol waivers or exemptions are not allowed.

Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.

The Investigator will maintain a Screening Log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

In the event of a significant trial-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

Safety, laboratory, and/or analyte results that could unblind the trial will not be reported to investigative sites or other blinded personnel.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

All procedures and assessments and laboratory tests (unless otherwise specified) will be done prior to administration of study intervention.

8.1. Efficacy Assessments

Efficacy measurements will be made at the times indicated in the Study Plan (see Table 2 for procedures and assessments to be performed at Screening and Table 3 and Table 4 for Treatment Period and Follow-Up).

The efficacy assessments based on laboratory tests include:

- Urine protein to creatinine ratio: This consists of:
    - **24-hour UPCR**: The 24-hour UPCR will be determined via a 24-hour urine sample.

      The 24-hour UPCR will be performed as follows: twice during the Screening Period, Weeks 0, 12, 24, 36, 48, 52, 64, 76, 88, 100, 104 and at ET Visits.

      During the Screening Period, two samples will be required:

        - Screening sample at the start of the Screening process (after the ICF is signed) and

- Stratification sample within 14 days prior to the expected day of Randomization and after a minimum of 10 days after the Screening sample was obtained. Without the results of the second sample, which will be used for stratification, participants cannot be randomized. Typical turn-around time for results from central laboratory is up to 7 days. On rare occasion, an extension of the 28-day screening window is allowed if the re-collection of the sample is necessary, or the results needed for Randomization are delayed.

Starting from Week 0 (Day 1), the 24-hour urine sample must always be collected before the administration of study intervention. The sample collected at Week 0 (Day 1) will be the baseline sample which must be provided on Day 1 prior to Randomization and administration of first dose of study intervention.

The collection of the 24-hour urine sample should start preferably in the morning of the day before the scheduled visit with the collection starting after the first void and end with the first void in the morning of the day of the visit. The urine collection may be done within 1 day prior to the visit if the urine sample can be kept refrigerated until the day of the visit.

The sample should be kept refrigerated whenever possible. If refrigeration is not possible, participants should select the coolest possible place to store their urine sample, eg, a cool room or use a portable cooler with ice/ice pack.

In the event that a participant has a medical reason which would impact the validity of the assessment of proteinuria (eg, urinary tract infection, heavy menstruation) or the sample was not collected appropriately, the collection of the sample may be completed/repeated as follows:

- Screening samples: As soon as possible before the next scheduled sampling is due.
- Week 0: Prior to study intervention administration (which may require the Day 1 Visit to be postponed).
- Weeks 12, 24, 36, 48, 52, 64, 76, 88, 100, and 104: Within 2 weeks of the actual date of the visit when the collection was due and, if applicable, before any changes in SOC or concomitant medications.

The 24-hour UPCR will be used for the primary and secondary endpoints, the PRR and CRR criteria at [redacted], and to determine withdrawal criteria at Weeks 12 and 24. [redacted].

- [redacted]

[redacted]

- [redacted]
- Estimated glomerular filtration rate based on the MDRD formula calculated by the central laboratory. Refer to the Laboratory Manual for further detail.

The efficacy assessments based on clinical evaluation include [redacted], OCS reduction, and SDI.

8.1.1. Training and Certification for Systemic Lupus Erythematosus Assessments

In order to maintain consistent evaluation of SLE assessments across study sites, training and certification of Investigators and designated site personnel who will be completing the disease evaluations listed below will be conducted.

- [redacted]
- [redacted]
- [redacted]
- SDI

These evaluations must be performed by the Investigator or another qualified physician, unless prior Sponsor approval has been obtained for any other clinically trained site personnel with documentation of adequate assessment experience.

After attending study presentations (ie, Investigator Meeting) or after completion of training modules, all Investigators and designated site physicians must pass an examination in order to obtain certification for all disease evaluation assessments. Investigators and designated site personnel must be trained and certified prior to participants entering the Screening Period at their respective sites. All assessments and certifications must be renewed via the study online training website prior to expiration and must remain current (not expire) throughout the course of the study. If there is a change in site personnel over the course of the study, new Investigators or physicians must be certified prior to performing the SLE assessments.

Documentation of all training will be maintained in the site's study file.

Over the course of the study, Investigator assessments for a given participant should be completed by the same trained and/or certified Investigator, designated physician, or qualified site personnel (as described above) whenever possible.

[redacted]

[redacted]

[redacted]

8.1.1.4. Systemic Lupus International Collaborating Clinics/American College Rheumatology Damage Index

The SDI has been developed to assess irreversible damage in SLE participants independently of its cause (ie, included damage due to SLE activity, SLE-related scarring, therapy, comorbidities) but occurring after disease onset. Damage, ie, irreversible impairment since onset of SLE, is usually defined as a clinical feature that must be continuously present for at least 6 months to score. In addition, some irreversible events such as myocardial infarction or a cerebrovascular accident, score as damage on their occurrence. Briefly, damage is defined for 12 organ systems: peripheral vascular, ocular, neuropsychiatric, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, skin, endocrine (diabetes), gonadal, and malignancies. Damage over time can be stable or increase, theoretically to a maximum of 47 points (Schwartz et al, 2009).

[redacted]

[redacted]

8.1.4. Renal Biopsy

Renal biopsy is required within 6 months prior to signing the ICF or during the Screening Period for inclusion into the study and must meet inclusion criterion No. 6 and not meet exclusion criterion No. 11. (Note: If a renal biopsy is performed during the Screening Period, adequate time should be allowed before the next scheduled urine sample collection). If a participant has not had a recent kidney biopsy within the 6 months prior to Screening, one may be performed to assess eligibility for the study provided informed consent has been given and results are received prior to Randomization. If one is performed as part of SOC after Randomization, the results will be recorded in the eCRF.

[redacted]

ADJUDICATION COMMITTEE

Renal Pathology Adjudication

Renal biopsies will be evaluated locally, and the local classification will be used to confirm the eligibility criteria. Screening biopsy slides or digital pathology images (ie, scanned slides) will then be submitted for adjudication post-randomization by an external renal pathology adjudication committee consisting of nephropathologists with special expertise in LN. The biopsies will be assessed for all elements of the ISN/RPS classification, the NIH activity, chronicity indices, and the presence of concomitant conditions. The submission of Screening biopsies for adjudication is required to participate in the study. The process for adjudication will be defined in a separate document (Renal Biopsy Adjudication Charter). [redacted]

[redacted]

Data Safety Monitoring Board

An external, independent Data Safety Monitoring Board (DSMB) will evaluate safety data at regular intervals throughout the trial and make recommendations to the Sponsor as needed. [redacted] This futility analysis is designed to be non-binding, so the DSMB may elect not to recommend terminating the trial after considering all of the data, even if the pre-specified futility criteria is met.

8.2. Safety Assessments

Safety assessments will include physical examinations, measurement of vital signs, electrocardiograms, and monitoring of hematology, blood chemistry, urinalysis, and local injection site assessment. Planned timepoints for all safety assessments are provided in the SoA (See Section 1.3).

8.2.1. Physical Examinations

The following sites/systems will at least be included in the focused physical examination, which will be performed at the visits specified in the SoA (Section 1.3):

- General appearance
- Dermatological
- Head, eyes, ears, nose, throat
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Information for all physical examinations must be included in the source document. If deemed appropriate by the Investigator, clinically significant findings in the Screening physical examination could exclude a participant from trial participation. Any significant change will be reported as an AE in the source document and eCRF.

8.2.2. Vital Signs

The following vital signs will be recorded at the visits specified in Section 1.3 with the participant in a seated or supine position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), body temperature (°C), and respiratory rate (breaths/minute).

Weight (kg) and height (cm) will be collected to calculate the body mass index (BMI) and will be recorded at the visits specified in 1.3. The height will only be recorded once at the Screening Visit and the same value will be used for BMI calculation at other visits.

If deemed appropriate by the Investigator, clinically significant findings in the vital signs will exclude a participant from trial participation. Any abnormal finding related to vital signs that the Investigator considers to be clinically significant must be recorded as an AE.

8.2.3. Electrocardiograms

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Section 1.3. Clinically significant findings in the ECG should exclude a participant from trial participation (as deemed appropriate by the Investigator). Any clinically significant value will be reported as an AE.

8.2.4. Clinical Laboratory Tests

Laboratory tests will be performed in a central laboratory at the visits specified in Section 1.3. The tests will include urinalysis, hematology with differential, a standard chemistry panel (including liver function tests), immunology, and a serum pregnancy test (Screening) for women of childbearing potential (WOCBP). At the visits specified in Section 1.3, a urine pregnancy test will be performed for WOCBP (conducted at the Investigator site). The specific tests in these panels are listed in Table 10.

[redacted]

[redacted]

In case of a screening laboratory value abnormality, the test may be repeated once within the original screening time window, if the Investigator believes there is a reasonable possibility that the participant would be eligible if re-tested.

If deemed appropriate by the Investigator, clinically significant findings in clinical laboratory testing will exclude a participant from trial participation. Any clinically significant value will be reported as an AE. The laboratory results must be retained with source documents.

8.2.5. Local Injection Site Assessment

Assessor local injection tolerability assessments will be performed approximately 30 minutes post-dose, at the visits specified in Section 1.3. The Investigator, or designee, will evaluate the injection sites at these visits, and will document the presence or absence of local intolerance/injection site reactions and will open an AE in case of local injection site intolerance. Additional follow-up after Week 100 will be performed for any ongoing injection site reactions during the SFU Period.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

8.3.1. Definitions

8.3.1.1. Definition of Adverse Event

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

8.3.1.2. Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the study intervention but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

8.3.1.3. Definition of Serious Adverse Event

A SAE or reaction is any untoward medical occurrence that, at any dose has any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Medically significant

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

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

Hospitalizations for elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, will not be classed as SAEs. Previously scheduled hospitalizations must be documented in the participant's source documents before the participant signed the ICF. A kidney biopsy performed as part of the study will not be considered an SAE. Any complication experienced during a kidney biopsy procedure resulting in hospitalization or a prolongation of the hospitalization requires SAE reporting.

8.3.1.4. Definition of an Adverse Event of Special Interest (AESI)

An AESI is an AE of scientific and medical interest specific to understanding of the study intervention and may require close monitoring and collection of additional information by the Investigator. An AESI may be serious or nonserious.

The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this study intervention.

The following AESIs will be particularly monitored in this trial:

- Hypersensitivity reaction, including anaphylaxis
- Severe viral infection/reactivation (CTCAE Grade 3 or higher)
- Opportunistic infection as listed in Appendix 2 (all cases)
- Malignancy (except non-melanoma skin cancer)

8.3.2. Classification of an Adverse Event

8.3.2.1. Relationship to Study Intervention

The Investigator is required to provide an assessment of the relationship of AEs and SAEs to the study intervention. An event will be considered "not related" to use of study intervention if any of the following are met:

- An unreasonable temporal relationship between administration of the study intervention and the onset of the event (eg, the event occurred either before, or too long after, administration of the study intervention for it to be considered study intervention related).
- A causal relationship between the study intervention and the event is biologically implausible (eg, death as a passenger in an automobile accident).
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event).

Individual AE/SAE reports will be considered "related" to use of the study intervention if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the study intervention (ie, there are facts, evidence, or arguments to suggest possible causation).

8.3.2.2. Adverse Event Severity

The guidelines outlined in CTCAE v5.0 will be used for assessing the severity or intensity of the event. The general guidelines for assessing the AE grade are provided in Table 11.

Table 11 CTCAE v.5.0 General Guidelines

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

Table 11 CTCAE v.5.0 General Guidelines

Grade	Description

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology for Adverse Events.
The CTCAE v5.0 is dated to 27 NOV 2017.
[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.3.2.3. Expectedness

Horizon Therapeutics Ireland DAC will assess the expectedness of each SAE in relation to the study intervention. Please refer to Investigator's Brochure for more details.

8.3.3. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of trial personnel during trial visits and interviews of a trial participant presenting for medical care, or upon review by a trial monitor.

All AEs, including local and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on trial must be documented appropriately regardless of relationship.

Trial site personnel will note the occurrence and nature of each participant's medical condition(s) present prior to the informed consent signature in the appropriate section of the source document and eCRF. During the trial, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present prior to informed consent signature will be considered as part of medical history and not reported as an AE. However, if the trial participant's condition deteriorates after the consent signature, it will be recorded as an AE.

Should a participant experience an AE at any time after the informed consent signature until the end of participation in the trial, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the trial participation (eg, screening procedure) will be recorded in the source document and eCRF from the time consent is given to participate in the trial until the end of participation in the trial.

The Investigator is responsible for appropriate medical care of participants during the trial. The Investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the trial. The participant should be followed until the event is resolved or stable. If an AE is ongoing at the end of trial, the follow-up duration is left to the discretion of the Investigator. Follow-up frequency will be performed at the discretion of the Investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

8.3.4. Adverse Event Reporting

Investigators are responsible for monitoring the safety of participants who are participating in this trial and for alerting the Sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

8.3.5. Serious Adverse Event Reporting

Horizon Therapeutics Ireland DAC will be the pharmacovigilance unit responsible for the overall pharmacovigilance process for this trial. All SAEs, related to the experimental treatment or not, occurring during the course of the trial must be reported by entering the information into the eCRF on an SAE form to the pharmacovigilance unit (see below contact information) within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned seriousness criteria). The SAE reporting period ends at the end of the Follow-Up Period or if the participant begins an alternative therapy.

Reporting should be done by sending the completed SAE form to the following e-mail address (faxing may also be done as a second option in case e-mailing is not possible).

Safety Contact Information: Horizon Therapeutics

E-mail: clinicalsafety@horizontherapeutics.com

US Fax: (800) 860 -7836

The pharmacovigilance unit will inform the Medical Monitor, the Sponsor, and the Contract Research Organization (CRO) within 1 business day of awareness of a new SAE. The pharmacovigilance unit will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the pharmacovigilance unit, in consultation with the Sponsor if needed, will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The expedited reporting of relevant safety information to concerned regulatory agencies and ethic committees will be performed in accordance with local laws and regulations and will be defined in the Safety Management Plan.

The trial Sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, the Sponsor must notify the FDA and all participating Investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

8.3.6. Pregnancy Reporting

If a female participant becomes pregnant during the trial, the participant should inform the trial site as soon as possible. Upon confirmation of the pregnancy, the female participant will be discontinued from the trial. If a female partner of a male participant becomes pregnant, the participant should inform the trial site as soon as possible. The Investigator must complete a trial-specific pregnancy form upon confirmation of a pregnancy and send it to the pharmacovigilance unit within 24 hours of confirmation of the pregnancy (contact information to be used is the same

as for SAE reporting). The pharmacovigilance unit will report all cases of pregnancy to the medical monitor, the Sponsor, and the CRO in a timely manner until completion of the pregnancy, until a healthy live-born offspring, or until the outcome of any abnormality. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The Investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. The Investigator will notify the pharmacovigilance unit and the CRO of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the Sponsor and, when applicable, to the ethics committee.

8.3.7. Overdose

Investigational Product overdose is any accidental or intentional use of study intervention in an amount higher than the dose indicated per protocol for a given participant. Study intervention compliance (see Section 6.5) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study intervention overdose during the trial should be recorded on the source document and eCRF. In the event of overdose, the participant should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 8.3.5, Serious Adverse Events Reporting, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the SAEs reporting procedures and in an expedited manner but should be noted as non-serious on the form and the Adverse Event eCRF. The excess quantity and duration of the overdose should be recorded.

8.4. Pharmacokinetics

Blood samples will be collected in serum separator collection tubes to evaluate PK at the following visits: pre- and 6 hours (± 1 hour) post-injection on Day 1, prior to SC administration on Weeks 2, 4, 8, 12, 16, 20, 24, 36, 48, 52, 64, 76, 88, 100, and 104; a single sample will be collected at the End-of-Study Visit.

PK samples will be collected, processed, and stored at the site until shipment to the central laboratory. The central laboratory will store the samples at ≤ -70ºC until shipment to the appropriate laboratory for testing.

Instructions for processing, handling, storing, and shipping of PK samples will be detailed in a Laboratory Manual that will be provided to each site prior to site initiation.

[redacted]

[redacted]

Samples may be stored for up to 15 years after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by sponsor or others such as universities or other companies to contribute to the understanding of LN or other diseases, the development of related or new treatments, or research methods.

8.8. Immunogenicity Assessments

Daxdilimab immunogenicity will be assessed by the incidence and titer of anti-drug antibodies prior to the daxdilimab administration and at specified time points. Number and percentage of participants who develop positive ADA will be summarized by treatment group. The potential association of ADA with safety and efficacy may be explored if data allow.

The detection and characterization of antibodies to study intervention will be performed using a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to study intervention.

Instructions for processing, handling, storing, and shipping of antidrug antibody samples will be detailed in a Laboratory Manual that will be provided to each site prior to site initiation.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The statistical hypotheses are as follows:

1. Null hypothesis (H_0): difference in proportion of responders (daxdilimab vs placebo) = 0
2. Alternative hypothesis (H_a): difference in proportion of responders (daxdilimab vs placebo) ≠ 0

9.2. Sample Size Determination

A sample size of approximately 210 participants (up to approximately 70 participants per treatment group) is planned for this trial. The sample size was calculated based on the primary efficacy endpoint. Assuming a placebo response rate of 25%, 70 participants per treatment group will provide approximately 80% power to detect an increase in response of 20% in either arm of a daxdilimab group as compared to the placebo group at the 2-sided alpha level of 0.10 using a Chi-square test. The minimum detectable difference is 13% between the daxdilimab group and placebo group. The assumption of 25% responder rate for placebo is based upon published results (Mejia-Vilet et al, 2021).

9.3. Analysis Sets

Analysis Populations:

Full Analysis Set: The Full Analysis Set will include all randomized participants who receive any dose of study intervention in the study. Participants will be analyzed according to the treatment randomized. The efficacy analysis will be based on the Full Analysis Set.

Safety Analysis Set: The Safety Analysis Set will include all participants who receive any dose of study intervention in the study. Participants will be analyzed according to the treatment that they actually received. Safety, PD, and ADA analyses will be based on Safety Analysis Set.

PK Analysis Set: The PK Analysis Set will include all participants who receive any dose of daxdilimab in the study and have at least one quantifiable serum PK observation post first dose. Participants will be analyzed according to the treatment that they actually received. The PK analysis will be based on the PK Analysis Set.

9.4. Statistical Analyses

9.4.1. General Considerations

Continuous variables will be summarized in tables and will include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages. Details of the statistical analysis will be specified in a separate SAP.

9.4.2. Primary Endpoint Analysis

9.4.2.1. Analyses of the Primary Efficacy Endpoint:

The estimand of primary interest is defined as follows, using composite variable strategy to address intercurrent events.

1. Population: Participants in the Full Analysis Set.
2. Variable (outcome measure): CRR at [redacted]. CRR is defined by meeting the following criteria:
    a. eGFR ≥60 mL/min/1.73m^2 or no worse than 15% below baseline.
    b. 24-hour UPCR ≤0.5 mg/mg.
    c. No use of restricted medication beyond the protocol allowed threshold before assessment.
    d. No discontinuation of study intervention.
3. Intercurrent event:
    a. Rescue medications: Captured in the primary variable definition.
    b. Treatment discontinuation: Captured in the primary variable definition.
4. Population-level summary: Difference in proportions of responders between the daxdilimab group and placebo group.

The proportion of participants achieving CRR at [redacted] in the daxdilimab group will be compared to that of the placebo group using a logistic regression model with treatment, baseline eGFR value and baseline UPCR value included in the model. The difference in proportions of responders of daxdilimab vs placebo will be estimated together with its associated 2-sided 90% confidence interval (CI).

9.4.2.2. Control of Type I Error

The type I error rate will be controlled at 0.1 level (2-sided) for the primary efficacy analysis using a fixed sequence testing procedure.

1. The primary endpoint will be tested for Daxdilimab [redacted] mg compared with placebo.
2. If p-value is ≤ 0.1 in step 1, the primary endpoint will be tested for Daxdilimab [redacted] mg compared with placebo.

9.4.3. Secondary Endpoints Analysis

The estimand for the binary secondary efficacy endpoints is defined as follows, using composite variable strategy to address intercurrent events.

1. Population:
    a. ORR: Participants in the Full Analysis Set.
    b. Sustained reduction of OCS dose: Participants in the Full Analysis Set whose Baseline OCS dose is greater than 2.5 mg/day prednisone equivalent.
2. Variable (outcome measure):

a. ORR at [redacted] which is an CRR or PRR at Week 52. PRR is defined by meeting the following criteria:
    i. eGFR ≥60 mL/min/1.73m^2 or no worse than 15% below baseline.
    ii. Improvement in 24-hour UPCR:
        – For participants with a baseline UPCR ≤3.0 mg/mg: <1.0 mg/mg
        – For participants with a baseline UPCR >3.0 mg/mg: >50% improvement from baseline and ≤3.0 mg/mg
    iii. No use of restricted medication beyond the protocol allowed threshold before assessment.
    iv. No discontinuation of study intervention.
b. Response in sustained reduction of OCS dose, which is defined by meeting the following criteria:
    i. Prednisone-equivalent dose ≤2.5 mg/day by Week 24 and not exceeding this dose through Week 52.
    ii. No use of restricted medication beyond the protocol allowed threshold before assessment.
    iii. No discontinuation of study intervention.

3. Intercurrent event:
    a. Rescue medications: Captured in the variable definition.
    b. Treatment discontinuation: Captured in the variable definition.
4. Population-level summary: Difference in proportions of responders between the daxdilimab group and placebo group.

ORR will be analyzed using a logistic regression model with treatment, baseline eGFR value and baseline UPCR value included in the model. Response in sustained reduction of OCS dose will be analyzed similarly using a logistic regression model with treatment, randomization stratification factors and baseline OCS dose included in the model.

The estimand of change from baseline in eGFR at Week 52 is defined as follows, using hypothetical strategy to address intercurrent event of rescue medications and treatment policy strategy to address intercurrent event of treatment discontinuation.

1. Population: Participants in the Full Analysis Set.
2. Variable (outcome measure): Change from baseline in eGFR at Week 52.
3. Intercurrent event:
    a. Rescue medications: The data collected after administration of the rescue medications will be excluded.

    b. Treatment discontinuation: Participants who discontinue study intervention will be asked to come to scheduled evaluations until the end of study. The data collected after discontinuation of study intervention will be included in the analysis.

2. The population-level summary: Mean difference between the daxdilimab group and placebo group.

Change from baseline in eGFR will be analyzed using mixed models for repeated measures (MMRM) with treatment, visit, visit by treatment interaction, randomization stratification factor (UPCR only), and baseline eGFR value included in the model.

[redacted]

9.4.5. Handling Plan for Missing Data:

For the categorical endpoint, the intermittent missing data will be imputed using last observation carried forward approach (LOCF). Participants with missing outcomes due to early discontinuation from the study will be considered as non-responders. If any of the criteria cannot be evaluated at a visit, that criterion will be imputed using LOCF. For the continuous endpoint, the missing data will be handled using the MMRM approach.

9.4.6. Safety Analyses

AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent AEs will be summarized by the number of participants reporting the events, as well as by System Organ Class, Preferred Term (PT), severity, seriousness, and relationship to study intervention. For the summary of AEs by severity, each participant will be counted only once within a System Organ Class or a PT by using the AEs with the highest intensity within each category. For the summary of AEs by relationship to study intervention, each participant will be counted only once within a System Organ Class or a PT by using the AEs with the greatest reported relationship within each category. The number and percentage of participants reporting treatment-emergent SAEs and treatment-emergent AESIs will also be summarized.

Clinically significant changes in laboratory analyses, vital signs, ECGs, and new findings on physical examination will be recorded as AEs or SAEs. Laboratory assessments, vital signs, and ECGs, as well as their changes from Baseline at each visit will also be summarized descriptively.

9.4.7. Pharmacokinetic Analyses

Serum concentrations will be summarized descriptively by treatment and by visit and the mean (±SD) serum concentration versus scheduled time profiles will be presented graphically.

Individual serum concentration vs. actual time profiles for each participant will be listed.

[redacted]

9.4.9. Planned Analyses

[redacted]

9.4.9.2. Planned Primary Analysis

The primary analysis will be conducted after the last participant has completed the Week 52 Visit or discontinued from study early. For the primary analysis, all the efficacy and safety data collected prior to the data cut-off will be analyzed.

9.4.9.3. Planned Final Analysis

The final analysis will be conducted after all participants have completed Week 112 Visit or discontinued early from the study.

10. REGULATORY, ETHICAL, AND TRIAL OVERSIGHT CONSIDERATIONS

10.1. Local Regulations/Declaration of Helsinki

This trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Tripartite Guideline for GCP and the applicable laws and regulations of the country in which the research is conducted, whichever affords greater protection to the individual.

10.2. Ethical Review

It is the understanding of the Sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by a research ethics board (REB)/ institutional review board (IRB). This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the Investigator to the Sponsor (or CRO) before initiation of the trial and also whenever subsequent modifications to the protocol are made.

10.3. Informed Consent Process

An ICF describing in detail the study intervention, trial procedures, and risks will be given to the participant, along with an assent form when required.

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this trial, after adequate explanation of the aims, methods, objectives, and potential hazards of the trial.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the trial and continues throughout the individual's trial participation. Consent forms will be IRB/REB approved, and the participant will be asked to read and review the document. The Investigator will explain the research trial to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the trial and of his or her rights as a research participant. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the trial with their family or surrogates or think about it prior to agreeing to participate.

The participant will sign the informed consent document prior to any procedures being done specifically for the trial. Participants must be informed that participation is voluntary and that they may withdraw from the trial at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any trial-specific procedures.

The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this trial.

If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a participant to continue to participate, the consent form should, if necessary, be reviewed and updated by the IRB/REB. All

participants (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the trial.

10.4. Trial Discontinuation and Closure

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for trial suspension or termination, will be provided by the suspending or terminating party to trial participants, Investigators, the Sponsor, and regulatory authorities. If the trial is prematurely terminated or suspended, the principal Investigators will promptly inform trial participants and the IRB/REB and will provide the reason(s) for the termination or suspension. Trial participants will be contacted, as applicable, and be informed of changes to trial visit schedule.

Circumstances that may warrant termination or suspension of the trial include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or corporate reasons

The trial may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB/REB, and applicable regulatory authorities.

10.5. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the trial protocol, documentation, data, and all other information generated will be held in strict confidence.

The Investigator must assure that the participants' anonymity will be maintained, and that participants' identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, participants should not be identified by their names, but by an identification code. The Investigator should keep a participant log relating codes with the names of participants. The Investigator should maintain in strict confidence documents not for submission to Horizon Therapeutics Ireland DAC (eg, participants' written consent forms).

All research activities will be conducted in a setting as private as possible.

The trial monitor, other authorized representatives of the Sponsor, and representatives of the IRB, regulatory agencies, or pharmaceutical company supplying IP may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.

The trial participant's contact information will be securely stored at each clinical site for internal use during the trial. At the end of the trial, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing

IRB, institutional policies, or Sponsor requirements.

10.6. Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Centralized monitoring, which consists of remote review of accumulating data from all sites, will be performed as detailed in the Centralized Monitoring Plan.

10.7. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of trial conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

During the trial, the Sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, IP accountability, compliance with regulatory requirements, and continued adequacy of the trial site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the Sponsor, by the REB or IRB, and/or by the regulatory authorities. The Investigator will be given notice before an audit occurs and will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested. The trial site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor and inspection by local and regulatory authorities.

10.8. Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The Investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. These documents should be classified into two separate categories: Investigator's study files and participant clinical source documents.

The Investigator must maintain source documents for each participant in the trial. These source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments. All information on the eCRFs must be traceable to the source documents in the participant's file. Data not requiring a written or electronic record will be defined before trial start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The records should be retained by the Investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Participant data will be entered by site personnel using electronic data capture (EDC). This application will be set up for remote entry. Fully validated EDC software conforming to Title 21 of the Code of Federal Regulations, Part 11 requirements will be utilized in this study. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated Investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the Investigator staff before confirming the data. The Investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the Sponsor.

10.9. Biological Specimens and Data

Study data are protected by the use of a sample identification (SID) number, which is a number specific to the participant. The Investigator is in control of the information that is needed to connect a study sample to a participant; a participant may withdraw consent at any time by notifying the Investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the Sponsor, but no new data or samples will be collected unless specifically required to monitor the safety of the participant.

Leftover samples stored for future research with participant consent will be labeled with a sample identification number. If the participant consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The participant's sample(s) will be stored by the Sponsor with similar samples in a secure laboratory. The participant's samples will not be kept for more than 15 years after the end of the study in which they were collected. If the participant chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the Sponsor once they are no longer required for the main study. If future use consent is withdrawn, the Sponsor and the Investigator will ensure that the participant's sample(s) are destroyed unless the identification number has been removed and the participant can no longer be linked to any samples. However, if the participant's sample has already been used for research, the Sponsor is not required to destroy the results of this research. In this case, only the remaining sample(s) will be destroyed.

10.10. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The non-compliance may be either on the part of the participant, the Investigator, or the trial site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. The CRA must ensure that a prompt action is taken to secure compliance. If a non-compliance that significantly affects or has the potential to significantly affect human participant protection or reliability of trial results is discovered, the CRO and the Sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions

Protocol deviations must be sent to the reviewing IRB per their policies. The Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.11. Publication Policy

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The trial will be registered on ClinicalTrials.Gov prior to the first participant being dosed.

11. REFERENCES

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12. APPENDIX

APPENDIX 1 NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE AND FOOD AND ALLERGY ANAPHYLAXIS NETWORK GUIDANCE FOR ANAPHYLAXIS DIAGNOSIS

National Institute of Allergy and Infectious Disease (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al, 2006). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (Category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), AND AT LEAST ONE OF THE FOLLOWING:

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory function [PEF], hypoxemia).
b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

a. Infants and children ─ low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure.
b. Adults ─ systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that participant's baseline.

APPENDIX 2 STUDY-SPECIFIED OPPORTUNISTIC INFECTIONS

Definite [a,b] Opportunistic Infection	**Probable [c] Opportunistic Infection**
Pneumocystis jirovecii	Paracoccidioides infections
BK virus disease, including polyomavirus-associated nephropathy	*Penicillium marneffei* (talaromyces)
CMV disease	Sporothrix schenckii
Post-transplant lymphoproliferative disorder (EBV)	Cryptosporidium species (chronic disease only)
Progressive multifocal leukoencephalopathy	Microsporidiosis
Bartonellosis (disseminated disease only)	Leishmaniasis (visceral only)
Blastomycosis	Trypanosoma cruzi infection (Chagas's disease) (disseminated disease only)
Toxoplasmosis	Campylobacteriosis (invasive disease only)
Coccidioidomycosis	Shigellosis (invasive disease only)
Histoplasmosis	Vibriosis (invasive disease due to *Vibrio vulnificus)*
Aspergillosis (invasive disease only)	HCV progression
Candidiasis (invasive disease or pharyngeal)	
Cryptococcosis	
Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor, and Lichtheimia), *Scedosporium/Pseudallescheria boydii, Fusarium*)	
Legionellosis	
Listeria monocytogenes (invasive disease only)	
TB	
Nocardiosis	
Non-tuberculous mycobacterium disease	
Salmonellosis (invasive disease only)	
HBV reactivation	
Herpes simplex (invasive disease only)	
Herpes zoster (any form)	
Strongyloides (hyperinfection syndrome and disseminated forms only)	

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; TB = tuberculosis.

Source: Winthrop et al, 2015.

[a] Generally does not occur in the absence of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.

[b] Can occur in patients without recognized forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.

[c] Published data are currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy.

APPENDIX 3 2019 EUROPEAN LEAGUE AGAINST RHEUMATISM/AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION SYSTEM FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

β2GP1 = β2-glycoprotein 1; C = complement; dsDNA = double-stranded DNA; Hep-2 = human epithelial type 2 cells; SLE = systemic lupus erythematosus. Source: Aringer et al, 2019.

APPENDIX 4 INTERNATIONAL SOCIETY OF NEPHROLOGY AND THE RENAL PATHOLOGY SOCIETY (ISN/RPS) 2003 CLASSIFICATION OF LUPUS NEPHRITIS

Class I	**Minimal mesangial lupus nephritis**
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis**
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits
	May be a few isolated subephithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis[a]**
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis[b]**
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis

Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis**
	Global or segmental subephithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V lupus nephritis may occur in combination with class II or IV in which case both will be diagnosed
	Class V lupus nephritis show advanced sclerosis
Class VI	**Advanced sclerosis lupus nephritis**
	≥90% of glomeruli globally sclerosed without residual activity

Source: Weening et al, 2004

[a] Indicate the proportion of glomeruli with active and with sclerotic lesions.

[b] Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

APPENDIX 5 PREDISONE EQUIVALENT OF ORAL GLUCOCORTICOID DOSE

Glucocorticoid	**Prednisone Equivalent Dose**					
PO prednisone	5 mg	7.5 mg	10 mg	20 mg	30 mg	40 mg
Prednisolone	5 mg	7.5 mg	10 mg	20 mg	30 mg	40 mg
Methylprednisolone	4 mg	6 mg	8 mg	16 mg	24 mg	32 mg
Hydrocortisone	20 mg	30 mg	40 mg	80 mg	120 mg	160 mg
Cortisone	25 mg	37.5 mg	50 mg	100 mg	150 mg	200 mg
Triamcinolone	4 mg	6 mg	8 mg	16 mg	24 mg	32 mg

PO: oral(ly).

ie,

1 mg prednisone = 1 mg prednisolone

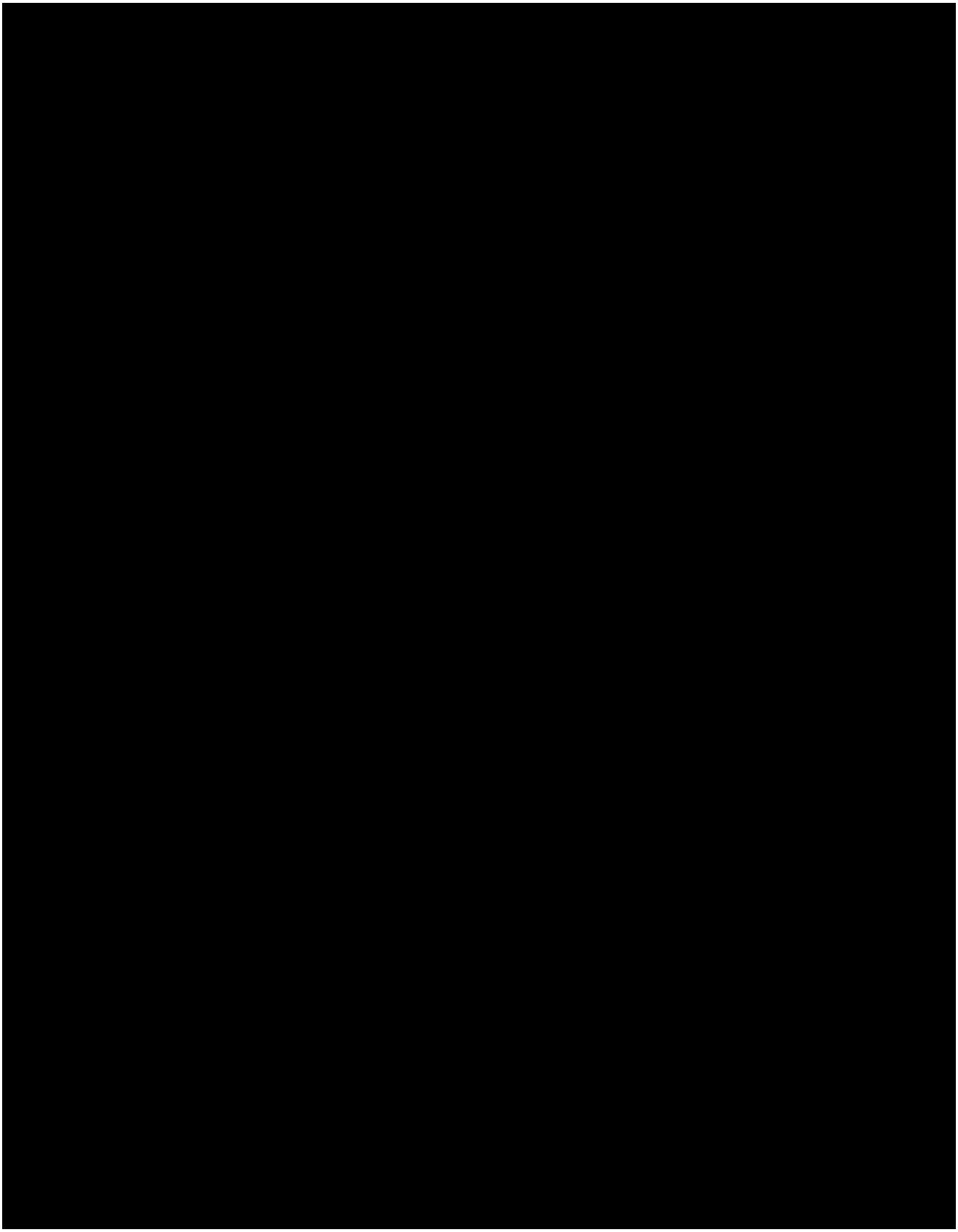
1 mg prednisone = 5 mg cortisone

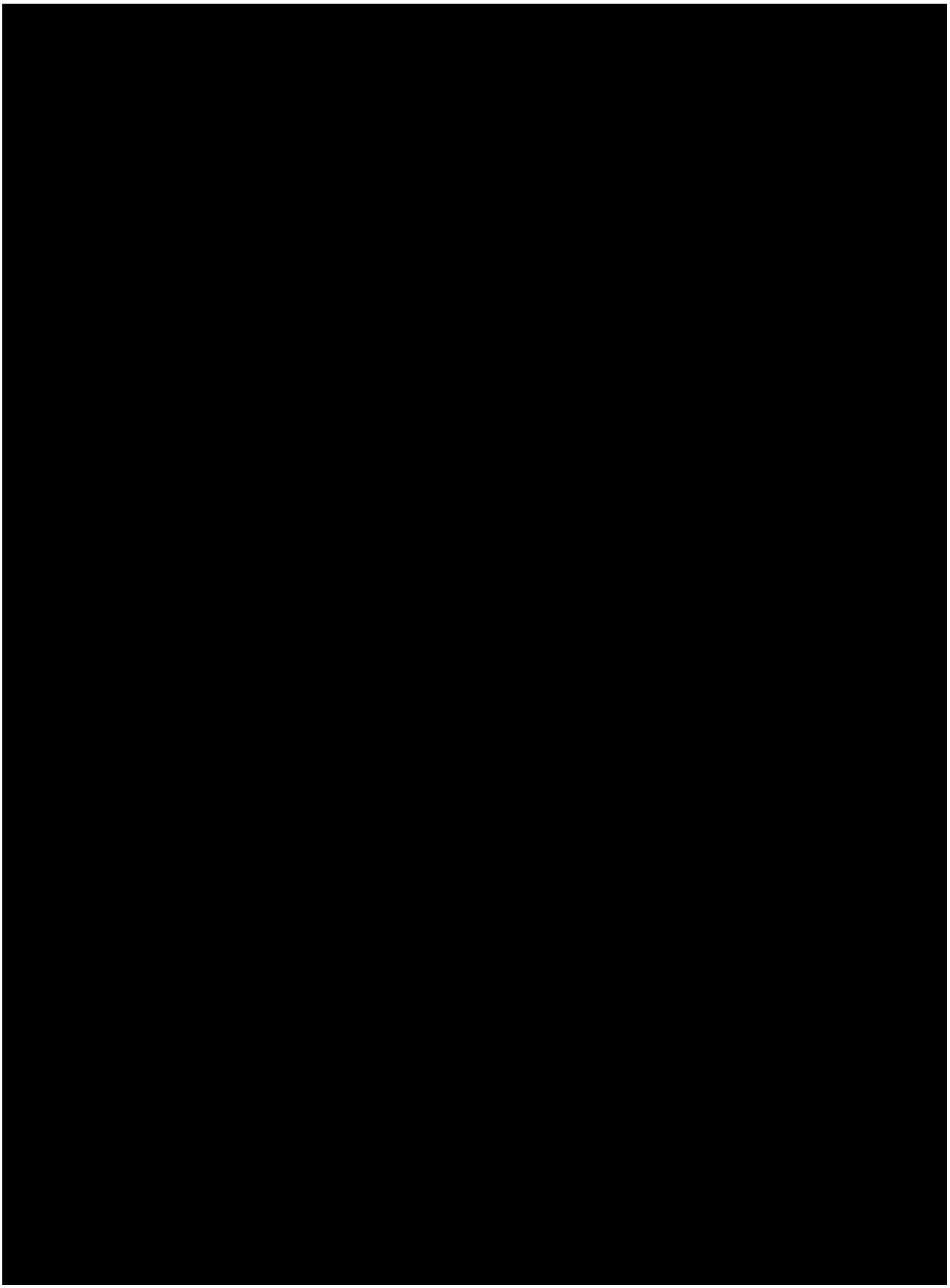
1 mg prednisone = 4 mg hydrocortisone (cortisol)

1 mg prednisone = 0.8 mg methylprednisolone

1 mg prednisone = 0.8 mg triamcinolone

1 mg prednisone = 0.15 mg dexamethasone





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