A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis

Clinical Protocol Number:	AUR-VCS-2016-01
Study Name:	AURORA (**AUR**inia **O**relvo **R**enal **A**ssessments) 1: Aurinia Renal Response in Active Lupus with Orelvo (voclosporin)
Date:	04 May 2017
Version Number:	2.0 (Amendment 1)
IND Number:	114577
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DECLARATION OF SPONSOR

Title: A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis

Version Number/Date: 2.0/04 May 2017

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the study treatment, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Council for Harmonisation Guidelines on Good Clinical Practice.

Sponsor Representatives

[redacted]

Vice President, Clinical Affairs

08 MAY 2017

Date (e.g., DD Month Year)

[redacted]

Vice President, Quality and Regulatory Affairs

08 May 2017

Date (e.g., DD Month Year)

INVESTIGATOR AGREEMENT FORM

I have read the attached protocol titled: *A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis.*

Version Number/Date: 2.0/04 May 2017

I agree to comply with the current International Council for Harmonisation Guidelines on Good Clinical Practice and applicable regulations and guidelines.

I agree to ensure that financial disclosure statements will be completed by:

- me (including, if applicable, my spouse (or legal partner) and dependent children);
- my sub-investigators

before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Aurinia Pharmaceuticals Inc.

Signature by the Investigator on this form documents review, agreement and approval of the requirements contained within this protocol.

Signature	Date (e.g., DD Month Year)

SYNOPSIS

Title:	A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis.
Short Title:	AURORA (**AUR**inia **O**relvo **R**enal **A**ssessments) 1: Aurinia Renal Response in Active Lupus with Voclosporin
Study Product:	Orelvo (voclosporin)
Indication:	Active lupus nephritis
Phase:	3
Sponsor:	Aurinia Pharmaceuticals Inc.
Study Code:	AUR-VCS-2016-01
Objectives:	Primary Objective: • To assess the efficacy of Orelvo (voclosporin) compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active lupus nephritis (LN) Secondary Objective: • To assess the safety and tolerability of Orelvo over 52 weeks compared with placebo in subjects with active LN
Design:	Prospective, randomized, placebo-controlled, double-blind, parallel-group, 52-week, international, multicenter, 2-arm comparison study of Orelvo versus matching placebo.
Treatment:	Investigational Treatment: Orelvo softgel capsules containing 7.9 mg drug. Approximately 324 subjects will be randomized to Orelvo (23.7 mg twice daily (BID)) or matching placebo (162 subjects per arm). All subjects will receive an initial treatment of intravenous (IV) methylprednisolone, followed by a reducing taper of oral corticosteroid. Additionally, all subjects will receive background therapy with mycophenolate mofetil (MMF). All subjects who complete participation and study treatment through 52 weeks and provide consent will have the opportunity to enroll into a continuation study (design pending finalization).
Inclusion Criteria:	1. Written informed consent before any study-specific procedures are performed. 2. Male or female subjects with a minimum age of 18 (or legal age of consent if >18 years) to 75 years of age, inclusive, at the time of screening (Visit 1). 3. Previous diagnosis of systemic lupus erythematosus (SLE) according to the American College of Rheumatology criteria (1997; see Appendix 5).

	4. Subjects with evidence of active nephritis, defined as follows: Kidney biopsy result within 2 years prior to screening indicating Class III, IV-S, IV-G (alone or in combination with Class V), or Class V LN (see Appendix 3) with a doubling or greater increase of urine protein creatinine ratio (UPCR) within the last 6 months to a minimum of ≥1.5 mg/mg for Class III/IV or to a minimum of ≥2 mg/mg for Class V at screening. Biopsy results over 6 months prior to screening must be reviewed with a medical monitor to confirm eligibility. OR Kidney biopsy result within 6 months prior to screening indicating Class III, IV-S, or IV-G (alone or in combination with Class V) LN with a UPCR of ≥1.5 mg/mg at screening. OR Kidney biopsy result within 6 months prior to screening indicating Class V LN and a UPCR of ≥2 mg/mg at screening. A biopsy can be performed during screening, if not available. The above criteria must be fulfilled at baseline. 5. In the opinion of the Investigator, subject requires high-dose corticosteroids and immunosuppressive therapy. 6. Subject is willing to take oral MMF for the duration of the study, either by continuing current MMF therapy or by initiating it on or before the Baseline Visit. 7. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline. Two effective forms of contraception must be used simultaneously unless abstinence is the chosen method. Subjects must use effective contraception during the study (see Section 5.4, Adequate/Effective Contraception).
Exclusion Criteria:	1. Subjects unable or unwilling to give written informed consent and/or to comply with study procedures. 2. Estimated glomerular filtration rate (eGFR) as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation of ≤45 mL/minute/1.73 m^2 at screening confirmed before randomization. 3. Currently taking or known need for any of the medications listed in Section 7.8, Prohibited Therapy and Concomitant Treatment at screening or during the study. This includes prohibited medications prior to screening as specified in Section 7.8.1, Prohibited Medications. 4. Currently requiring renal dialysis (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study period. 5. A previous kidney transplant or planned transplant within study treatment period.

6. Any known hypersensitivity or contraindication to MMF, mycophenolic acid, cyclosporine, corticosteroids or any components of these drug products.

7. Current or medical history of:

- Congenital or acquired immunodeficiency.
- In the opinion of the Investigator, clinically significant drug or alcohol abuse within 2 years prior to screening.
- Malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision. Subjects with cervical dysplasia that is cervical intraepithelial neoplasia 1, but have been treated with conization or loop electrosurgical excision procedure and have had a normal repeat Papanicolaou test are allowed.
- Lymphoproliferative disease or previous total lymphoid irradiation.
- Severe viral infection (e.g., cytomegalovirus, hepatitis B virus, hepatitis C virus) within 3 months of screening; or known HIV infection. Severe viral infection is defined as active disease requiring antiviral therapy.
- Active tuberculosis (TB), or known history of TB/evidence of old TB if not taking prophylaxis with isoniazid (see Section 9.2.1, Screening Visit Procedures).

8. Other known clinically significant active medical conditions, such as:

- Severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome. QT interval duration corrected for heart rate using method of Fridericia exceeding 480 msec in the presence of a normal QRS interval (<110 msec) at time of screening will result in exclusion.
- Liver dysfunction (aspartate aminotransferase, alanine aminotransferase, or bilirubin ≥2.5 times the upper limit of normal) at screening and, if abnormal at screening, then confirmed that the levels have returned to <2.5 times upper limit of normal before randomization.
- Chronic obstructive pulmonary disease or asthma requiring oral steroids.
- Bone marrow insufficiency unrelated to active SLE (according to Investigator judgment) with white blood cell count <2,500/mm^3; absolute neutrophil count <1.3 × 10^3/μL; thrombocytopenia (platelet count <50,000/mm^3).
- Active bleeding disorders.
- Current infection requiring IV antibiotics.

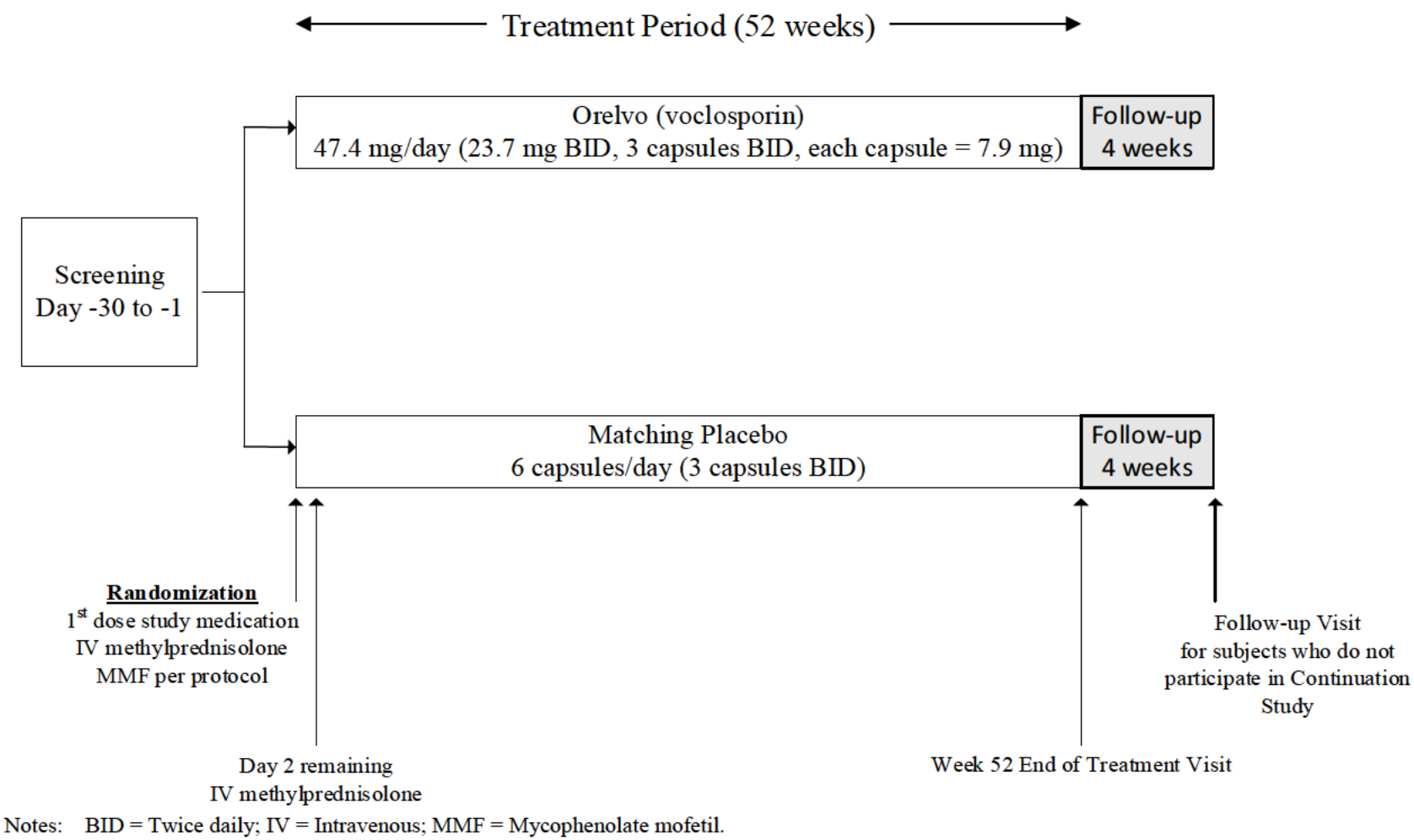
9. Any overlapping autoimmune condition for which the condition or the treatment of the condition may affect the study assessments or outcomes (e.g., scleroderma with significant pulmonary hypertension; any condition for which additional immunosuppression is indicated). Overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes (e.g., Sjögren's syndrome) are not excluded.

	10. No vaccines using live organisms, virus or bacterial, are allowed during screening and while taking the study treatment. 11. Other major physical or psychiatric illness or major traumatic injury within 6 months prior to screening that may affect study conduct or interfere with study assessments or outcome. 12. Any other medical condition which, in the Investigator's judgment, may be associated with increased risk to the subject or may interfere with study assessments or outcomes. 13. Subjects who are pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions. 14. Participation in another interventional clinical study within 4 weeks prior to screening and/or receipt of investigational drugs within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to screening. 15. Subjects randomized and treated in a previous voclosporin clinical study.
Primary Endpoint:	Renal response at Week 52 will be adjudicated by the Clinical Endpoints Committee based on the following parameters: • UPCR of ≤0.5 mg/mg, and • eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20%, and • Received no rescue medication for LN (see Section 7.8, Prohibited Therapy and Concomitant Treatment), and • Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52, just prior to the renal response assessment. Subjects who withdraw from the study prior to the Week 52 assessment will be defined as non responders.
Secondary Endpoints:	• Time to UPCR of ≤0.5 mg/mg. • Partial renal response as defined by 50% reduction from baseline in UPCR at Weeks 24 and 52. • Time to 50% reduction in UPCR from baseline. • Renal response at Week 52 (based on definition of primary endpoint). • Duration of UPCR ≤0.5 mg/mg. • Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each timepoint. • Change from baseline in UPCR at each time point. • Change from baseline in serum creatinine, urine protein, and eGFR.

	• Change from screening in immunology parameters (complement 3 (C3), C4, and anti-double-stranded DNA). • Renal response with low-dose steroids (defined as renal response in the presence of corticosteroids of ≤2.5 mg between Weeks 16 to 24 and Weeks 44 to 52). • Change from baseline in health-related quality of life at Weeks 12, 24, and 52. • Health Resource Utilization at Weeks 24 and 52. • Change from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity (SELENA-SLEDAI) Index score at Weeks 24 and 52.
Procedures:	See Schedule of Events for full details of protocol required procedures and applicable visits (and timings). Subjects who have provided signed and dated informed consent will be screened for entry into this study. Baseline proteinuria level is determined by a mean of 2 first morning void urine samples taken during the screening period. If a subject has not had a kidney biopsy within the required timeframe for study eligibility, one may be performed to assess eligibility into the study, provided consent is in place and provided the results are received before randomization. Subjects meeting the required eligibility criteria will be randomized in a ratio of 1:1 to receive either Orelvo (23.7 mg BID) or matching placebo starting on Day 1. All subjects will receive initial treatment with 0.5 to 1.0 g IV methylprednisolone. In consultation with the Medical Monitor, and if it is in the subject's best interest, IV methylprednisolone may be started during the screening period. Subjects receiving IV methylprednisolone in the 3 months prior to screening must be discussed with the Medical Monitor prior to initiating further IV methylprednisolone. For subjects 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 g/day for the first week, increasing to 1 g BID for a total daily dose of 2 g/day for the second and subsequent weeks (i.e., beginning on Day 8). All subjects will complete dosing through 52 weeks of study treatment. Subjects who permanently discontinue study treatment before the Week 52 visit will return for all remaining study visits and assessments unless they have withdrawn consent. All subjects who complete participation and study treatment through 52 weeks and provide consent will have the opportunity to enroll into a continuation study for which the details are not yet finalized.
Sample Size:	A 2 group continuity corrected Chi square test with a 0.05 two-sided significance level will have 80% power to detect the difference between a placebo response rate of 20.0% and an Orelvo response rate of 34.4% (odds ratio=2.1) when the sample size in each group is 162 (total N=324). While the effect of withdrawals will be investigated, subjects withdrawing for any reason will be counted as non-responders in the primary analysis and therefore no adjustment of sample size for withdrawals is necessary.

Statistical Methods:	Analysis: All statistical analyses will be undertaken at study closure and will incorporate all Week 24 and Week 52 endpoints. Populations: The efficacy analysis will be based on the intent-to-treat (ITT) principles and will consist of all randomized subjects. The per-protocol set will be a subset of subjects in the ITT population who do not have any major protocol violations (to be defined prior to unblinding). The safety analysis set will consist of all subjects who receive at least 1 dose of study treatment. Methods: The primary analysis of the primary endpoint, renal response at Week 52, will be conducted on the ITT population. The relative renal response for Orelvo compared to placebo will be determined using logistic regression. The logistic regression model will include terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline. Results of this logistic regression will be displayed as odds ratios and a 2-sided confidence interval (CI) (Orelvo compared to placebo). The proportion of subjects exhibiting renal response at Weeks 24 and 52 will be summarized by treatment group. The analyses of the secondary endpoints are described below: Other binary endpoints will be analyzed in a similar manner to the primary endpoint. Endpoints measured as a time-to-event will be displayed using Kaplan-Meier methodology. Orelvo will be compared to placebo using a Cox proportional hazard model. The model will include terms for treatment and appropriate baseline assessments. Median time-to-event along with 2-sided CIs will be displayed. Other endpoints will be summarized by visit and differences between baseline and on-treatment values at weeks up to and including Week 52 will be analyzed using Mixed Effect Model Repeated Measures (MMRM). The MMRM model will include terms for treatment, visit, treatment by visit interaction and baseline. Results will be expressed as differences between treatment arms (along with associated 95% CI). Safety Endpoints: Adverse events will be aggregated by System Organ Class and preferred term and presented as summary tables. Laboratory values (based on results from the central laboratory), vital signs and other safety parameters will be summarized by visit as absolute values and change from baseline. Laboratory values outside of defined normal ranges will be summarized. The impact of withdrawals on primary endpoint will be investigated with a tipping point analysis.

SCHEMA



Notes: BID = Twice daily; IV = Intravenous; MMF = Mycophenolate mofetil.

AUR-VCS-2016-01 SCHEDULE OF EVENTS

Visit[1]	**Visit 1 Screening**	**Visit 2 Baseline**	**Visit 3**	**Visits 4-8**	**Visit 9**	**Visit 10**	**Visits 11-13**	**Visit 14**	**Visit 15 End of Treatment/ Early Termination**[2]	**Visit 16 Safety Follow-up**[3]
Day/Week	**Day -30 to Day -1**	**Day 1**	**Day 2**	**Wks 2, 4, 8, 12, 16 ±3 days**	**Wk 20 ±3 days**	**Wk 24 ±10 days**	**Wks 30, 36, 42 ±10 days**	**Wk 48 ±10 days**	**Wk 52 ±10 days**	**Wk 56 ±10 days**
Informed consent	✓									
Eligibility criteria	✓	✓								
Kidney biopsy[4]			See footnote[4]							
Randomization		✓								
Medical/Surgical/SLE/LN history	✓									
Demography	✓									
Physical examination[5]	✓	✓				✓			✓	
Vital signs (BP, pulse, temperature)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECG[6]	✓			✓[7]		✓			✓	
Laboratory assessments[8]	✓	✓		✓	✓	✓	✓	✓	✓	✓
Pharmacokinetics[9]						✓			✓	
Urinalysis	✓	✓		✓	✓	✓	✓	✓	✓	✓
FMV urine collection	✓[10]			✓	✓	✓	✓	✓	✓	✓
24-hour urine[11]	✓					✓			✓	

Visit[1]	**Visit 1 Screening**	**Visit 2 Baseline**	**Visit 3**	**Visits 4-8**	**Visit 9**	**Visit 10**	**Visits 11-13**	**Visit 14**	**Visit 15 End of Treatment/ Early Termination**[2]	**Visit 16 Safety Follow-up**[3]
Day/Week	**Day -30 to Day -1**	**Day 1**	**Day 2**	**Wks 2, 4, 8, 12, 16 ±3 days**	**Wk 20 ±3 days**	**Wk 24 ±10 days**	**Wks 30, 36, 42 ±10 days**	**Wk 48 ±10 days**	**Wk 52 ±10 days**	**Wk 56 ±10 days**
Pregnancy test[12]	✓	✓		✓	✓	✓	✓	✓	✓	
AEs[13]		✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications[14]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SELENA-SLEDAI		✓				✓			✓	
SF-36 and LupusPro[15]		✓		✓[7]		✓			✓	
Healthcare Resource Utilization[16]		✓				✓			✓	
Dispense study treatment/compliance		✓		✓	✓	✓	✓	✓	✓[17]	
First dose of study treatment (at the study site)[18]		✓								
MMF dispensing[19]		✓		✓	✓	✓	✓	✓	✓	
IV methylprednisolone administration[20]		✓	✓							
Oral corticosteroid tapering[21]				✓						

1 Unscheduled visits/assessments can be done as needed. Adverse events, concomitant medications and verbal compliance check is needed.

2 Subjects who discontinue study treatment or terminate the study early, are to attend an Early Termination Visit and have the assessments listed performed. Subjects who complete study treatment will attend the End of Treatment at Week 52 and have the assessments listed performed.

3 Subjects who do not enroll into the continuation study will have a follow up safety visit 4 weeks after the last dose of study treatment.

4 If a subject has not had a recent kidney biopsy, 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 standard of care after randomization, the results will be recorded in the electronic case report form.

5 Complete physical examination at screening, abbreviated examination at all other applicable visits. Height is measured at screening only.

6 During the study, and after screening, in the event that a subject is noted to have a QTcF value exceeding 500 msec, or >60 msec more than baseline, the ECG will be repeated; see Section 9.1.4.1, Procedures to Manage a Treatment-Emergent Increase in QTc. Electrocardiograms will be recorded digitally after the subject has been in a resting, supine position for at least 5 minutes.

7 Week 12 only.

8 Laboratory assessments will be performed according to the schedule in Section 9.1.1, Laboratory Assessments; subjects must be fasting for at least 8 to 12 hours at baseline and end of study/early termination.

9 Blood samples will be collected at 0 and 2 hours post dose for pharmacokinetics.

10 Two FMV specimens, to be performed and resulted before baseline.

11 24-hour urine collection should begin 2 days prior to the scheduled study visit in order not to coincide with the FMV sampling due on the day of the study visit.

12 Serum pregnancy test to be evaluated at central laboratory at screening, Week 24, and Week 52; urine pregnancy test will be performed locally at all other applicable visits.

13 Adverse events will be recorded after the subject signs the ICF; AEs which occur during screening or prior to the first dose of study treatment will not be considered TEAEs.

14 Concomitant medications include all herbal medicines and supplements taken by the subject.

15 For details on HRQoL assessments, see Section 9.3.1, Health-related Quality of Life Assessments (HRQoL).

16 For details on Healthcare Resource Utilization, see Section 9.3.2, Healthcare Resource Utilization Assessment.

17 Compliance only.

18 All scheduled procedures must be done prior to first dose, including IV methylprednisolone and MMF.

19 For subjects not on MMF during screening, will start receiving MMF therapy at the Baseline Visit and return for local complete blood count assessments at Weeks 1 and 3 after randomization (see Section 7 2 2 3, Mycophenolate Mofetil (Background Therapy)).

20 IV methylprednisolone administered 0.5 g on baseline and Day 2. If IV corticosteroids must be administered during screening then the FMV urine specimens will be collected prior to the infusion (see Section 7.2.2.2, Corticosteroids).

21 See Section 7.2.2.2, Corticosteroids.

Notes: Subjects who discontinue therapy will attend their regularly scheduled study visits to the end of the study. Subjects who withdraw consent and terminate the study early or discontinue treatment early should be advised to attend both Visit 15 and the Safety Follow up Visit (Visit 16).

Abbreviations: AE=adverse event; BP=blood pressure; CBC=complete blood count; ECG=electrocardiogram; FMV=first morning void; HRQoL=health-related quality of life; IV=intravenous; LN=lupus nephritis; MMF=mycophenolate mofetil; QTcF=QT interval duration corrected for heart rate using method of Fridericia; SAE=serious adverse event; SELENA-SLEDAI=Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; SLE=systemic lupus erythematosus.

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ADR	Adverse drug reaction
AE	Adverse event
ALMS	Aspreva Lupus Management Study
ANC	Absolute neutrophil count
ARB	Angiotensin receptor blocker
AUC_{0-12}	Area under the curve between 0 and 12 hours
AUC_{0-24}	Area under the curve between 0 and 24 hours
AURA-LV	**A**urinia **U**rinary protein **R**eduction **A**ctive – **L**upus with **V**oclosporin
AURION	**A**urinia early **U**rinary protein **R**educt**ION** Predicts Response
AURORA	**AUR**inia **O**relvo **R**enal **A**ssessments
Aurinia	Aurinia Pharmaceuticals Inc.
AZA	Azathioprine
BID	Twice daily
BP	Blood pressure
C3 / C4	Complement 3 / complement 4
CEC	Clinical Endpoints Committee
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum concentration
CNI	Calcineurin inhibitor
CsA	Cyclosporine A
CYP3A4/5	Cytochrome P450 3A4/5
DMC	Data Monitoring Committee
dsDNA	Double-stranded deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee

EDC	Electronic data capture
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FAS	Full analysis set
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HCP	Health care professional
HIV	Human immunodeficiency virus
HR	Heart rate
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVC	Intravenous cyclophosphamide
IWRS	Interactive web response system
LN	Lupus nephritis
MMF	Mycophenolate mofetil
MMRM	Mixed Effect Model Repeated Measures
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
Orelvo	Voclosporin (for Phase 3 lupus nephritis indication)
P-gp	P-glycoprotein

PK	Pharmacokinetic
QTc	Corrected QT interval
QTcF	QT interval duration corrected for heart rate using method of Fridericia
SAE	Serious adverse event
SAP	Statistical analysis plan
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
$t_{1/2}$	Terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
UPCR	Urine protein creatinine ratio
[redacted]	[redacted]
WHO	World Health Organization

1. INTRODUCTION AND BACKGROUND

1.1 Background of the Disease and Treatment Options – Lupus Nephritis

Lupus nephritis (LN) is the most common serious manifestation of systemic lupus erythematosus (SLE). Lupus nephritis is divided into different classes according to the level of treatment required, using a classification system for renal biopsy pathology originally developed by the World Health Organization (WHO). The classification of LN has evolved and the "International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis" is now widely used and has a higher level of inter-observer reproducibility than the original classification (see Appendix 3). For subjects with Class III, IV (proliferative), or V (membranous), or combinations of these forms of LN, the standard of care is treatment with corticosteroids and immunosuppressive therapy.

Lupus nephritis manifests as diverse patterns of immune complex-mediated renal disease affecting glomerular, tubulointerstitial, and vascular compartments. It can lead to permanent and irreversible tissue damage within the kidney, resulting in end-stage renal disease (ESRD), and thus making LN a serious and potentially life-threatening condition. In subjects with LN, renal damage results in proteinuria and/or hematuria and a decrease in renal function as evidenced by reduced creatinine clearance and estimated glomerular filtration rate (eGFR), and increased serum creatinine levels.

In LN as in other serious renal diseases, the main clinical outcomes are progression to ESRD (i.e., the need for long-term dialysis or transplantation) and death. The current standard of care for LN, corticosteroids and immunosuppressants, has improved the prognosis of the disease considerably. Incidence rates of ESRD in LN, however, appear to have been stable over recent years, possibly reflecting the limits of effectiveness of current treatments or lack of adherence to treatments by subjects. The most recent studies have reported 10-year survival rates of over 90% and, although the overall risk of developing ESRD in subjects with LN is approximately 15%, the 5-year risk of developing ESRD has been found to be as low as 5% [1]. Recently, 10-year follow-up data of LN subjects treated with intravenous cyclophosphamide (IVC) for active disease followed by maintenance treatment with azathioprine (AZA) found rates of ESRD to be approximately 7% [2].

1.1.1 Limitations of Current Treatment

The current treatment paradigm for LN includes 2 goals, based on the severity of disease. The first goal of treatment in subjects with active LN is intended to bring the disease under control as quickly as possible to limit the potential for extensive renal scarring or loss of life. This phase of treatment is particularly critical for those subjects at highest risk for ESRD (i.e., subjects with clinical or laboratory indicators of active nephritis, such as biopsy evidence of

proliferative nephritis, active urinary sediment, elevated serum creatinine, and/or proteinuria). In subjects with severe LN, the achievement of complete or partial remission, as demonstrated by stabilization or improvement in renal function, improvement in proteinuria, and normalization of active urinary sediment, has been shown to be associated with better patient and renal survival. Treatment of active LN (i.e., induction treatment) typically consists of high doses of both corticosteroids and immunosuppressants.

The second goal of treatment, after the patient successfully responds to treatment, is to maintain remission by preventing renal flares and any resulting deterioration in renal function. In this second phase of treatment, lower doses of both corticosteroids and immunosuppressants are used.

Corticosteroids are the cornerstone of treatment in SLE, and have been the standard since the 1950s to treat both renal and non-renal manifestations. Intravenous (IV) steroid pulse therapy is widely used to rapidly treat relapsing LN, but does not provide long-term management. Oral corticosteroids taken for prolonged periods and at high doses are often needed, but have potentially severe, and at times irreversible adverse effects including risk of infection, hyperlipidemia, hypertension, osteoporosis, diabetes, and accelerated atherosclerosis. Induction treatment recommendations advocate the use of immunosuppressants in conjunction with high-dose oral corticosteroids, to enable a rapid taper to a lower maintenance dose of steroids. Steroid-sparing therapies are needed in order to treat disease activity and also minimize cumulative and high-dose steroid exposure.

Intravenous cyclophosphamide, while classically considered the standard of care for induction therapy, is still associated with significant potentially life-threatening toxicities, such as the increased risk of severe infections including sepsis, malignancy, and major morbidity, such as permanent gonadal failure.

Recent studies have shown that induction treatment with mycophenolate mofetil (MMF) has similar efficacy to that of IVC. The authors of a recent meta-analysis concluded that MMF is as efficacious as IVC and is not associated with the risk of infertility, which is a significant toxicity of IVC in this patient population [3]. In the Aspreva Lupus Management Study (ALMS), a comparison of MMF and IVC in the treatment of active LN, 50.4% subjects with active LN entering the study had nephrotic-range proteinuria (>3 g/day) [4]. Intravenous cyclophosphamide and MMF reduced proteinuria to a similar extent. However, even after 24 weeks of therapy with either MMF or IVC in the setting of a clinical study, subjects had substantial residual proteinuria. At the end of 24 weeks of therapy, normal (<500 mg/24 hours) protein excretion levels were observed in only 27% of subjects who received IVC and 23.8% of subjects who received MMF [5]. The findings from ALMS indicate that there exists a substantial unmet medical need for more effective treatments for active LN with heavy proteinuria.

The importance of proteinuria and reduction of proteinuria as prognostic factors for renal flares, ESRD and death in subjects with LN is well documented. Proteinuria in itself is related to progression of renal disease through effects on the glomerulus and tubulointerstitium [6]. In observational studies, proteinuria has been shown to be a predictor of adverse renal outcomes, cardiovascular disease, and mortality in subjects with non-diabetic proteinuric nephropathies [7].

1.2 Rationale for the Use of Calcineurin Inhibitors in Lupus Nephritis

1.2.1 Mechanism of Action

Calcineurin inhibitors (CNIs) are a class of immunosuppressants which reversibly inhibit immunocompetent lymphocytes, particularly T-lymphocytes in the G_0 and G_1 phase of the cell-cycle, and also reversibly inhibit the production and release of lymphokines. Voclosporin, a CNI, mediates its suppressive effects by binding to an ubiquitous intracellular protein cyclophilin. This complex, in turn, inhibits the calcium- and calmodulin-dependent serine/threonine phosphatase activity of the enzyme calcineurin. Calcineurin inhibition then prevents the activation of various transcription factors necessary for the induction of cytokine genes during T-cell activation, such as interleukin-2, interleukin-4, tumor necrosis factor-α, granulocyte-macrophage colony stimulating factor, and interferon-γ.

1.2.2 Use of Immunosuppression in Lupus Nephritis

Calcineurin inhibitors are standard treatment to prevent acute rejection in subjects who have received transplants. Since the development of cyclosporine in the early 1980s, standard immunosuppression regimens to prevent rejection post-transplantation have included steroids and a CNI; more recently other immunosuppressants, such as MMF, have been added to standard therapy. The rationale for use of CNIs in autoimmune diseases include potent effects on T-cell activation and immunomodulatory effects. AT-cell mediated immune response is an important feature of the pathogenesis of many of these diseases, including LN. Calcineurin inhibitors also have specific anti-proteinuric effects. The podocyte is a key cell in the glomerular capillary wall that maintains the integrity of the filtration barrier and prevents the development of proteinuria in healthy individuals, while being the primary target of injury in proteinuric kidney disease. Podocyte injury is an important factor in the progression of LN. It typically occurs due to immune complex deposition but may also occur in the absence of this histologic feature [8]. Podocyte function depends on a complex and unique structure that, in turn, depends on a tightly regulated actin cytoskeleton. Synaptopodin acts as a key stabilizer of the actin cytoskeleton in podocytes. When synaptopodin is phosphorylated, it binds to another protein, 14-3-3, and is thus protected from degradation. Calcineurin dephosphorylates synaptopodin allowing its degradation, thus promoting proteinuria by destabilization of the podocyte actin cytoskeleton. Expression of activated calcineurin in podocytes leads to proteinuria. By inhibiting activated calcineurin, tacrolimus thus exerts a specific

anti-proteinuric effect by preventing the degradation of the podocyte-stabilizing protein synaptopodin. Taken together, these data suggest that the anti-proteinuric effects of CNIs may be explained by their direct effect on the podocyte actin cytoskeleton as well as immunomodulatory effects on T-lymphocytes [9].

1.2.3 Clinical Studies of Calcineurin Inhibitors in Lupus Nephritis

Bao et al, 2008 [10] performed an open-label study in 40 subjects with Class V+IV LN. Subjects were randomized to either IVC and prednisolone or "multi-target therapy" with MMF plus tacrolimus (4 mg/day) and prednisolone. In the multi-target group, 50% achieved complete remission compared with 5% in the standard IVC group at 6 months. Estimated glomerular filtration rate normalized in both groups, but there was a significantly larger reduction in proteinuria in the multi-target therapy group.

Miyasaka et al, 2009 [11] evaluated the efficacy and safety of tacrolimus in 63 subjects receiving glucocorticoid therapy for LN in a double-blind, placebo-controlled, randomized trial. Subjects with persistent nephritis requiring 10 mg/day prednisone were randomized to receive 28 weeks of treatment with tacrolimus (3 mg/day) or placebo. There was a statistically significant improvement in the primary endpoint, the Lupus Nephritis Disease Activity Index, in the tacrolimus group compared to the placebo group. Daily urinary protein excretion (the percentage of subjects with urine protein <0.3 g/day at the final evaluation) also showed a significant decrease in the tacrolimus group. However, measures of glucose intolerance were more frequent in tacrolimus-treated subjects. The authors concluded that tacrolimus should be considered one of the options to treat LN. On the basis of the results of this study, tacrolimus was approved for the treatment of LN in Japan.

In an observational study conducted by Cortes-Hernandez et al, 2010 [12], 70 subjects who had received MMF as continuous therapy were followed over a 5-year period. Tacrolimus was added as rescue therapy in 17 subjects who were treatment failures or had renal flares on treatment with MMF. The authors reported a significant reduction in proteinuria at 3 months, and after 2 years of follow-up, it was concluded that tacrolimus was a safe and effective treatment for MMF non-responsive cases.

Several smaller pilot studies and case series in subjects with LN, including subjects with membranous nephropathy, have suggested a treatment benefit of tacrolimus with or without MMF [13-19].

The available data suggest a plausible mechanism of action by which CNIs may provide treatment benefits in LN. The clinical evidence is suggestive of improvement in measures of response in active LN and improvement in extrarenal manifestations of SLE and immunologic parameters.

1.2.4 Voclosporin

Voclosporin is a next-generation CNI developed for the treatment of autoimmune diseases and for use in the prevention of organ graft rejection. Voclosporin is structurally similar to cyclosporine A (CsA) except for a novel modification of a functional group on the amino acid 1 residue of the molecule. This alteration has changed the binding of voclosporin to calcineurin leading to a 3- to 5-fold increase in potency when compared to CsA. This modification has also shifted metabolism away from amino acid 1, the major site of metabolism for CsA, thus altering the metabolic profile. This in turn has led to faster elimination of metabolites resulting in lower measured metabolite exposure as compared to CsA. The combination of increased potency and decreased measured metabolite exposure, for voclosporin as compared to CsA, has led to better pharmacokinetic (PK)/ pharmacodynamic predictability.

During the development of this investigational product the legacy names of voclosporin, VCS, [redacted] are referenced in discussions related to historical usage. However, for the LN Phase 3 clinical development program, the name of the investigational product will be referred to as Orelvo, the proposed trade name. These legacy names should all be considered interchangeable unless specifically identified as different.

Prior to the LN clinical development program, approximately 2,200 subjects received investigational products containing voclosporin in 14 Phase 1 and 10 Phase 2/3 clinical studies in the indications of transplant rejection, psoriasis and non-infectious uveitis. Detailed data for these clinical studies are presented in the Investigator's Brochure (IB).

1.2.4.1 Pharmacokinetic Considerations

Voclosporin approximates linear multiexponential PKs. Exposure to voclosporin was dose-related with maximum concentrations occurring ≤2 hours with a terminal elimination half-life ($t_{1/2}$) of ≥30 hours. Drug accumulation was minor with accumulation factors of approximately 2 hours after twice daily (BID) dosing. Administration of voclosporin oral solution with either low- or high-fat meals decreased both the rate and extent of absorption which appeared to be related to the fat content of the meal. It is therefore recommended that Orelvo (voclosporin) be administered on an empty stomach to ensure adequate absorption.

Voclosporin has been shown to be a substrate of cytochrome P450 3A4/5 (CYP3A4/5). Concomitant administration of ketoconazole, a strong CYP3A4/5 inhibitor, led to a 6-fold increase in maximum concentration (C_{max}) and an 18-fold increase in area under the curve between 0 and 12 hours (AUC_{0-12}) for voclosporin. Concomitant administration of rifampin, an inducer of CYP3A4/5, resulted in a decrease in exposure to voclosporin. Maximum concentration decreased approximately 70%, the area under the concentration curve decreased approximately 90%, and $t_{1/2}$ decreased 85%. Consequently, both ketoconazole and rifampin are contraindicated with Orelvo (voclosporin). Concomitant administration of voclosporin and

midazolam, a model substrate of CYP3A4/5 and potential inhibitor of CYP3A4/5, did not result in statistically significant changes in the rate or extent of exposure to midazolam or α-hydroxy-midazolam.

Voclosporin is both a substrate for and an inhibitor of P-glycoprotein (P-gp). Concomitant administration of verapamil, a known inhibitor of P-gp, demonstrated an approximate 3-fold increase in C_{max} and AUC_{0-12} of voclosporin. Concomitant administration of digoxin, a P-gp substrate, resulted in statistically significant increases in digoxin C_{max} and area under the curve between 0 and 24 hours (AUC_{0-24}) and a decrease in clearance. Therefore concomitant administration of P-gp substrates with voclosporin would be expected to result in increased exposure to the substrate. Clinicians are advised to consider the benefit/risk of concomitant P-gp substrate drugs carefully.

1.2.4.2 Lupus Nephritis Clinical Development

The AURA-LV study (Protocol AUR-VCS-2012-01) is a randomized, controlled, double-blind Phase 2 study comparing the efficacy and safety of voclosporin (23.7 mg BID or 39.5 mg BID) with placebo in achieving remission in patients with active LN. The duration of the study is 48 weeks and is ongoing. All patients received background therapy with MMF and corticosteroid taper. The primary endpoint of complete remission was defined as: urine protein creatinine ratio (UPCR) of ≤0.5 mg/mg at 24 weeks (using first morning void) and eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of ≥20%. In addition, patients could not receive rescue medications for LN (defined as >10 mg prednisone/day for >3 consecutive days or >7 days total from Weeks 16-24) to be considered for complete remission.

A total of 265 subjects were randomized into the AURA-LV study. The 24-week primary endpoint assessment for the AURA-LV clinical study demonstrated that the groups were generally well balanced for age, gender and race, with a trend to higher proteinuria and lower eGFR data in the low-dose voclosporin arm. The low dose achieved a statistically significant benefit over placebo for the primary efficacy assessment of complete remission at 24 weeks (odds ratio (OR) [95% CI] = 2.03, [1.01, 4.05], p=0.045), without a statistically significant improvement seen in the high dose. The results were confirmed by 24 hour urine collections (p=0.047). Both the low- and high-dose voclosporin were statistically superior to placebo in partial remission, time to complete remission, and time to partial remission. A mean reduction in serum creatinine was seen in both arms (0.2 mg/dL low, 0.1 high; p<0.001). In the voclosporin groups, eGFR fell by a median of 8-9 mL/min by Week 4 and then stabilized over the course of the study. Blood pressure did not vary by group. The correlation of 24-hour urine protein and using the first morning void was assessed from the results of the AURA-LV study demonstrating a high degree of correlation (Pearson Correlation Coefficient = 0.92).

Over 90% of subjects experienced at least 1 adverse event (AE); the most common being infectious disease (56.2% low-dose, 63.6% high-dose and 50.0% placebo), GI disorders (41.6% low-dose, 52.3% high-dose and 36.4% placebo). More serious adverse events (SAEs) occurred in the voclosporin groups (25.8% low-dose, 25.0% high-dose, 15.8% placebo), and were consistent with those observed in LN patients. There were 13 deaths (4.9%) during the study. There were more deaths in the voclosporin low-dose arm (10) than in either the voclosporin high-dose (2) or placebo (1) arms, with the majority (11/13) occurring in Asia. All deaths were assessed by the Investigators as unrelated to study treatment.

In summary, no unexpected safety signals were observed with the use of voclosporin in LN subjects; voclosporin was generally well tolerated. The overall safety profile is consistent with the expectations for the class of drug, the patient population, and concomitant therapies.

The AURION study (protocol AUR-VCS-2014-01) is an exploratory open-label Phase 2 study assessing the short-term predictors of remission of voclosporin 23.7 mg BID in combination with standard of care in patients with active LN. The duration of the study is 48 weeks with 10 subjects randomized. All subjects received background therapy with MMF and corticosteroids. At 24 weeks, 4/7 (57.1%) subjects continued to be in complete remission as measured by a UPCR of ≤0.5 mg/mg, eGFR within 20% of baseline, and concomitant steroid dose of less than 5 mg/day. Within these 7 AURION patients, there was a 54% mean reduction in proteinuria at 24 weeks compared to pre-treatment levels along with consistent improvements in complement 3 (C3), C4 and anti-double-stranded DNA. Renal function as measured by eGFR remained stable. Voclosporin was well tolerated with no unexpected safety signals observed.

1.2.5 Potential Toxicities

Voclosporin has been studied in numerous disease states. When examining LN, there were a small proportion of voclosporin treated subjects that experienced an early drop of ≥30% in eGFR, however that proportion then remains stable over time. None of these treatment-emergent adverse events (TEAEs) were classed as serious. The majority of TEAEs of decreased GFR were classed as mild or moderate, and resulted in permanent discontinuation of study drug in 1 (1.1%) placebo subject, 6 (6.7%) voclosporin low-dose subjects and 5 (5.6%) voclosporin high-dose subjects. There were more TEAEs of hypertension seen in the voclosporin-treated patients compared to placebo however, overall mean systolic and diastolic blood pressure (BP) decreased in all groups, without statistically significant differences seen between groups. Overall, only 1 (1.1%) subject, in the voclosporin high-dose group, had a TEAE of hypertension that resulted in permanent discontinuation of study drug.

There was evidence of an increased incidence of TEAEs over placebo and with increased dose of voclosporin in the System Organ Classes of Infections and Infestations, Gastrointestinal Disorders, and Vascular Disorders.

There were more deaths in the voclosporin low-dose arm (10) than in either the voclosporin high-dose (2) or placebo (1) arms, with the majority (11/13) occurring in South-East Asia. All deaths were assessed by the Investigator and Data and Safety Monitoring Board (DSMB) as unrelated to study treatment. A full description of adverse events can be found in the IB.

2. RATIONALE

The rationale for the development of Orelvo and the choice of doses is to introduce a novel CNI to the LN patient population, with meaningful efficacy while minimizing toxicities common to other CNIs. In clinical studies, a favorable efficacy/safety profile for Orelvo has been demonstrated in the prevention of renal transplant rejection.

As evaluated in nonclinical and clinical studies (healthy volunteers, moderate to severe psoriasis, renal transplantation, and uveitis) Orelvo is well tolerated and exhibits AEs that are typical of other CNIs yet seen to a lesser extent than that seen historically with other CNIs.

The aim of the current study is to investigate whether Orelvo, added to the standard of care treatment in active LN, is able to reduce disease activity over a treatment period of 52 weeks. The background therapy will be MMF at a dose of at least 1 g/day and initial treatment with IV methylprednisolone, followed by a reducing course of oral corticosteroids. Subjects with active, flaring LN will be eligible to enter the study. They are required to have a diagnosis of LN according to established diagnostic criteria (American College of Rheumatology) and clinical and biopsy features suggestive of active nephritis. Efficacy will be assessed by the ability of the drug combination to reduce the level of proteinuria (as measured by urine protein/creatinine ratio (UPCR)) while demonstrating an acceptable safety profile. Normally, most subjects will respond to treatment by 6 months, but the optimal short-term predictor of long-term renal function is the response to treatment by 12 months (as observed in the AURA-LV study). Therefore, the primary endpoint of the Phase 3 study will be complete renal response at 52 weeks.

2.1 Dose Rationale

This Phase 3 study is designed to evaluate the treatment benefit of Orelvo 23.7 mg BID versus placebo. Orelvo and/or placebo are herein referred to as study treatment. The selection of Orelvo dose in this study (see Section 7, Study Treatments) was based on the previous experience with this drug in the Phase 2 study (AURA-LV). In AURA-LV, subjects were administered voclosporin 23.7 mg BID, 39.5 mg BID, or matching placebo. Low-dose voclosporin was significantly superior to placebo in the proportion of subjects achieving complete renal response at Week 24 (p=0.045). There was no increase in efficacy with the higher dose and no significant differences between the 2 voclosporin groups in achievement of renal response.

Orelvo 23.7 mg BID will be administered as a fixed dose without the use of therapeutic drug monitoring. Population PK analyses of voclosporin concentrations from the clinical development program (including healthy subjects, subjects with renal impairment, subjects with hepatic impairment, renal transplant, and plaque psoriasis) demonstrated that weight did not have a significant effect on the PKs of voclosporin. The protocol contains provisions for

management of dose based on safety concerns, in particular, BP and renal function. The safety data from the use of voclosporin demonstrates that these risks are dose-related, reversible, and can be managed by dose reduction and temporary interruption.

3. STUDY OBJECTIVES

3.1 Primary Objective

- To assess the efficacy of Orelvo (voclosporin) compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active LN

3.2 Secondary Objective

- To assess the safety and tolerability of Orelvo over 52 weeks compared with placebo in subjects with active LN

3.3 Endpoints

3.3.1 Primary Endpoint

Renal response at Week 52 will be adjudicated by the Clinical Endpoints Committee (CEC) based on the following parameters:

- UPCR of ≤0.5 mg/mg, and
- eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20%, and
- Received no rescue medication for LN (see Section 7.8, Prohibited Therapy and Concomitant Treatment), and
- Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52, just prior to the renal response assessment

Subjects who withdraw from the study prior to the Week 52 assessment will be defined as non-responders.

3.3.2 Secondary Endpoints

3.3.2.1 Key Secondary Endpoints

- Time to UPCR of ≤0.5 mg/mg
- Partial renal response as defined by 50% reduction from baseline in UPCR at Weeks 24 and 52
- Time to 50% reduction in UPCR from baseline
- Renal response at Week 52 (based on definition of primary endpoint)

- Duration of UPCR ≤0.5 mg/mg

- Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each timepoint

3.3.2.2 Other Secondary Endpoints

- Change from baseline in UPCR at each time point

- Change from baseline in serum creatinine, urine protein, and eGFR

- Change from screening in immunology parameters (complement 3 (C3), C4, and anti-double-stranded deoxyribonucleic acid (dsDNA)) at Weeks 24 and 52

- Renal response with low-dose steroids (defined as renal response in the presence of corticosteroids of ≤2.5 mg/day between Weeks 16 to 24 and Weeks 44 to 52)

- Change from baseline in health-related quality of life (HRQoL) at Weeks 12, 24, and 52

- Health Resource Utilization at Weeks 24 and 52

- Change from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity (SELENA-SLEDAI) Index score at Weeks 24 and 52

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 3, multicenter, randomized, prospective, double-blind, parallel-group, placebo-controlled, 2-arm comparison study of Orelvo versus matching placebo. Subjects who have provided a signed and dated informed consent will be screened into the study up to 30 days before randomization. During the screening period, eligibility criteria will be assessed. A kidney biopsy may be performed, provided the subject has given consent and provided the results can be obtained and reviewed before baseline. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for randomization into the study.

Baseline assessments will be performed before the first dose of study treatment is administered on Day 1. The baseline assessments of the serum creatinine and urine protein laboratory parameters will be established by using the mean of the 2 pre-randomization values. Using an interactive web response system (IWRS), eligible subjects will be randomized to receive either oral Orelvo 23.7 mg BID or matching placebo for 52 weeks. All subjects should receive 0.5 g/day IV methylprednisolone on Days 1 and 2 before changing to a reducing course of oral corticosteroid therapy on Day 3. (For additional details and exceptions, see Section 7.2.2.2, Corticosteroids). Starting at the Baseline Visit, all subjects will also receive background therapy with MMF (see Section 7.2.2.3, Mycophenolate Mofetil (Background Therapy).

All subjects will return for assessment of efficacy and safety at Day 2 and Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 52. See Schedule of Events, for detailed information regarding visits. In addition, subjects not on MMF during screening, will start receiving MMF at the Baseline Visit and will return for local complete blood count assessments at Weeks 1 and 3 after randomization.

All subjects, completed or withdrawn, will complete the End of Treatment/Early Termination assessments (Visit 15) at Week 52 or at the time of early termination. Subjects who do not enroll in the continuation study will attend the Safety Follow-up Visit (Visit 16) at Week 56 to collect any new AEs and concomitant medications. At the follow-up visit, UPCR and eGFR will be assessed as well. For subject withdrawal procedures and criteria, see Section 5.5, Withdrawal of Subjects.

4.2 Duration of Subject Participation and Study

The expected duration of subject participation is approximately 60 weeks. The screening period is up to 30 days and the treatment duration is 52 weeks, with a further follow-up visit 4 weeks after last dose (completion or early termination) if not participating in the continuation study.

5. SELECTION, WITHDRAWAL OF SUBJECTS AND PERMANENT DISCONTINUATION OF DRUG

5.1 Number of Subjects

It is anticipated that approximately 324 subjects (162 in the Orelvo 23.7 mg BID treatment group and 162 subjects in the placebo group) will be randomized in this study.

5.2 Inclusion Criteria

The following inclusion criteria must be met for each subject:

1. Written informed consent before any study-specific procedures are performed.

2. Male or female subjects with a minimum age of 18 (or legal age of consent if >18 years) to 75 years of age, inclusive, at the time of screening (Visit 1).

3. Previous diagnosis of SLE according to the American College of Rheumatology criteria (1997; see Appendix 5).

4. Subjects with evidence of active nephritis, defined as follows:

   Kidney biopsy result within 2 years prior to screening indicating Class III, IV-S, IV-G (alone or in combination with Class V), or Class V LN (see Appendix 3) with a doubling or greater increase of UPCR within the last 6 months to a minimum of ≥1.5 mg/mg for Class III/IV or to a minimum of ≥2 mg/mg for Class V at screening. Biopsy results over 6 months prior to screening must be reviewed with a medical monitor to confirm eligibility.

   OR

   Kidney biopsy result within 6 months prior to screening indicating Class III, IV-S, or IV-G (alone or in combination with Class V) LN with a UPCR of ≥1.5 mg/mg at screening.

   OR

   Kidney biopsy result within 6 months prior to screening indicating Class V LN and a UPCR of ≥2 mg/mg at screening.

   A biopsy can be performed during screening, if not available. The above criteria must be fulfilled at baseline.

5. In the opinion of the Investigator, subject requires high-dose corticosteroids and immunosuppressive therapy.

6. Subject is willing to take oral MMF for the duration of the study, either by continuing current MMF therapy or by initiating it on or before the Baseline Visit.

7. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline. Two effective forms of contraception must be used simultaneously unless abstinence is the chosen method. Subjects must use effective contraception during the study (see Section 5.4, Adequate/Effective Contraception).

5.3 Exclusion Criteria

1. Subjects unable or unwilling to give written informed consent and/or to comply with study procedures.

2. eGFR as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation of ≤45 mL/min/1.73 m^2 at screening confirmed before randomization.

3. Currently taking or known need for any of the medications listed in Section 7.8, Prohibited Therapy and Concomitant Treatment at screening or during the study. This includes prohibited medications prior to screening as specified in Section 7.8.1, Prohibited Medications.

4. Currently requiring renal dialysis (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study period.

5. A previous kidney transplant or planned transplant within study treatment period.

6. Any known hypersensitivity or contraindication to MMF, mycophenolic acid, cyclosporine, corticosteroids or any components of these drug products.

7. Current or medical history of:

   - Congenital or acquired immunodeficiency.

   - In the opinion of the Investigator, clinically significant drug or alcohol abuse within 2 years prior to screening.

- Malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision. Subjects with cervical dysplasia that is cervical intraepithelial neoplasia 1, but have been treated with conization or loop electrosurgical excision procedure, and have had a normal repeat Papanicolaou test are allowed.

- Lymphoproliferative disease or previous total lymphoid irradiation.

- Severe viral infection (e.g., cytomegalovirus, hepatitis B virus, hepatitis C virus) within 3 months of screening; or known HIV infection. Severe viral infection is defined as active disease requiring antiviral therapy.

- Active TB, or known history of TB/evidence of old TB if not taking prophylaxis with isoniazid (see Section 9.2.1, Screening Visit Procedures).

8. Other known clinically significant active medical conditions, such as:

    - Severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome. QT interval duration corrected for heart rate using method of Fridericia (QTcF) exceeding 480 msec in the presence of a normal QRS interval (<110 msec) at time of screening will result in exclusion.

    - Liver dysfunction (aspartate aminotransferase, alanine aminotransferase, or bilirubin ≥2.5 times the upper limit of normal) at screening and, if abnormal at screening, then confirmed that the levels have returned to <2.5 times upper limit of normal before randomization.

    - Chronic obstructive pulmonary disease or asthma requiring oral steroids.

    - Bone marrow insufficiency unrelated to active SLE (according to Investigator judgment) with white blood cell count <2,500/mm^3; absolute neutrophil count (ANC) <1.3 × $10^3/\mu L$; thrombocytopenia (platelet count <50,000/mm^3).

    - Active bleeding disorders.

    - Current infection requiring IV antibiotics.

9. Any overlapping autoimmune condition for which the condition or the treatment of the condition may affect the study assessments or outcomes (e.g., scleroderma with significant pulmonary hypertension; any condition for which additional immunosuppression is indicated). Overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes (e.g., Sjögren's syndrome) are not excluded.

10. No vaccines using live organisms, virus or bacterial, are allowed during screening and while taking the study treatment.

11. Other major physical or psychiatric illness or major traumatic injury within 6 months prior to screening that may affect study conduct or interfere with study assessments or outcome.

12. Any other medical condition which, in the Investigator's judgment, may be associated with increased risk to the subject or may interfere with study assessments or outcomes.

13. Subjects who are pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions.

14. Participation in another clinical study within 4 weeks prior to screening and/or receipt of investigational drugs within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to screening.

15. Subjects randomized and treated in a previous voclosporin clinical study.

5.4 Adequate/Effective Contraception

Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline. Two effective forms of contraception must be used simultaneously unless abstinence is the chosen method. Effective contraception must be used before beginning study treatment, during study dosing, and for 6 weeks following discontinuation of study treatment or MMF dosing, even when there has been a history of infertility, unless due to surgical sterilization. Women not of childbearing potential are defined as women without menses for at least 12 consecutive months or surgically sterilized.

Sexually active men, both reproductively competent and vasectomized, are required to use condoms during treatment and for at least 90 days after cessation of study treatment or MMF. In addition, female partners of male subjects are recommended to use an effective contraception during their partner's treatment and for at least 90 days after the last dose of study treatment or MMF. Male subjects are to refrain from making sperm donations during treatment and for at least 90 days after cessation of study treatment or MMF.

An effective and medically acceptable method of birth control means the chance of pregnancy, when using that type of birth control, is less than 1% per year if used correctly. These birth control methods (i.e., reliable forms of contraception) include birth control pills (combined oral contraceptives), hormone implants, hormone shots, and some intrauterine contraceptive devices. The use of MMF in this study can also reduce the effectiveness of the oral contraceptive pill.

Barrier methods (e.g., condoms, diaphragm, or cervical cap/sponge) when used alone are not highly considered effective.

Although abstinence, when adhered to, is an effective method of birth control, other additional effective contraception methods should be used where there is any doubt. The method of contraception needs to be discussed with the Investigator throughout the study period in order to confirm the method used is considered effective.

5.5 Withdrawal of Subjects

Subjects may voluntarily withdraw from study participation at any time for any reason. Alternatively, subjects may be withdrawn at the Investigator's discretion if it is in the subject's best interest.

Every effort should be made for subjects who withdraw from the study, either voluntarily or at the Investigator's discretion, to undergo end of study assessments (Visit 15), if possible. If possible, the subject should also be advised to come for the Safety Follow-up Visit 4 weeks after last dose. If a subject refuses end of study procedures, the reason for refusal should be fully documented in the subject's source document and recorded in the study specific electronic case report form (eCRF). It is the subject's right to withdraw from the study without providing a reason. In this case, the source documents and the eCRF should document the reason for discontinuation as "withdrawal of consent." Withdrawn subjects will not be replaced.

5.6 Discontinuation of Study Treatment

If any subject is discontinued from study treatment, the reason for discontinuation will be documented in the eCRF. If the reason for discontinuing study treatment is an AE or an abnormal laboratory test result, the specific event or test will be recorded in the eCRF. Except for cases involving pregnancy, subjects who are discontinued from study treatment should undergo all study assessments up to and including (Week 52 or Early Termination Visit – Visit 15), if possible. The subject should also be advised to come for the Safety Follow-up Visit 4 weeks after last dose. Guidance on when study treatment must be discontinued is in Section 7.6, Orelvo/Placebo Dose Modification.

5.6.1 Discontinuation from Study Treatment Due to Early Non-response to Therapy

Subjects will be discontinued from study treatment if their early disease response is suboptimal. The Investigator must contact the Medical Monitor to discuss further continuation in the study if the subject meets 1 of the 2 following criteria:

- After 12 weeks of treatment, the subject shows a >30% decrease from baseline value in CKD-EPI eGFR in 2 successive measurements separated by at least 4 weeks

or

- After 8 weeks of treatment, the subject shows a confirmed reduction in UPCR of ≤25% assessed by 2 consecutive measurements at least 2 weeks apart.

If the subjects require treatment with IV methylprednisolone or any rescue medication other than that permitted in the protocol (see Section 7.2.2.2, Corticosteroids), they should be permanently discontinued from the study treatment and will be considered a treatment failure. Subjects who are permanently discontinued from study treatment will be treated as deemed appropriate by the Investigator.

5.6.2 Discontinuation of Study Treatment Due to an Adverse Event

Subjects may be permanently discontinued from study treatment because of the appearance of an unacceptable AE. It is vital to obtain follow-up data on any subject withdrawn because of an AE. In any case, every effort must be made to evaluate protocol-specified safety follow-up procedures (see Section 10.3, Reporting Procedure for AEs, SAEs, and Pregnancy). If a subject is withdrawn due to an AE, the event should be followed by the Investigator through contact with the subject until resolution or stabilization has occurred. All AEs should be followed until resolution, stabilization or the subject is lost to follow-up and cannot be contacted.

6. RANDOMIZATION, BLINDING AND UNBLINDING PROCEDURES

6.1 Randomization

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and subject names to enable records to be found at a later date. Subjects will be allocated a subject number at the screening visit and registered with an interactive central randomization system. Subjects meeting the required eligibility criteria will be randomized to treatment at Visit 2 (baseline). The randomization will be stratified by biopsy class (Class V only versus Others) and by prior MMF use at time of screening. The subjects will be randomized in a ratio of 1:1 to receive either Orelvo 23.7 mg BID or matching placebo. To help ensure balance, a centralized randomization will be utilized where region will be employed as a blocked factor.

Details on randomization procedures will be provided in a separate manual.

6.2 Blinding

In order to preserve the double-blind design, subjects randomized to the placebo group will be matched to the active dosage groups. Dosing schedule in the placebo group will be the same as that of the active treatment group. To this end, the double-blind nature of this study preserves the blind with respect to active study treatment and placebo.

All study personnel and subjects will be blinded to the study treatment administered during the study. Orelvo and placebo will be identical in taste, smell, and appearance. The randomization code key will not be available to the Study Monitors, project statisticians or the project team at Aurinia Pharmaceuticals Inc. (Aurinia) or its representatives. The site staff, monitors, and study subjects will remain blinded until the end of the study. In case of emergency, the unblinding process below should be followed.

6.3 Unblinding

In the rare event that an AE or pregnancy occurs for which knowledge of the identity of the study treatment administered is necessary to manage the subject's condition, the IWRS code for that subject may be broken and the test substance identified. Procedures for unblinding will be provided in a separate manual.

Should emergency unblinding be required, the Investigator should call the [redacted] Medical Monitor before unblinding wherever possible; however, the Investigator is responsible for the medical care of the individual study subject, and does not require the agreement of the Medical Monitor before unblinding. The reason for unblinding must be documented. The information on study treatment should only be used for decision

making in the subject's further treatment. Details on unblinded treatment assignments should not be shared with the Study Monitor and project team.

7. STUDY TREATMENTS

7.1 Dosage Forms/Formulation

All study treatment to be used in this study will be manufactured in accordance with current Good Manufacturing Practice (GMP). Study treatment will be supplied by Aurinia.

7.1.1 Orelvo– Study Treatment

Company Code: [redacted]

Chemical Name: [redacted]

Empirical Formula: [redacted]

Generic Name: Voclosporin

Dosage Form: Softgel capsules

Strength: 7.9 mg of voclosporin per softgel capsule

Manufacturer: [redacted]

7.1.2 Placebo Control

Placebo softgel capsules, identical to 7.9 mg Orelvo softgel capsules, will be provided.

7.1.3 Background Therapy

7.1.3.1 Mycophenolate Mofetil

Oral MMF in the form of 500 mg tablets will be centrally supplied by Aurinia. Aurinia will reimburse the cost of the MMF tablets if not centrally provided by Aurinia to the sites.

7.1.3.2 Corticosteroids

Intravenous and oral corticosteroids will be prescribed at the investigational sites and costs will be reimbursed by Aurinia.

7.2 Drug Dosage and Administration

7.2.1 Treatment Arms

All subjects will receive either 3 capsules of Orelvo (23.7 mg BID) or matching placebo BID.

Orelvo – 23.7 mg (3 capsules) BID

Orelvo 23.7 mg BID; 3 capsules administered BID in combination with MMF and oral corticosteroids from randomization onwards.

Placebo – 3 capsules BID

Placebo; 3 capsules administered BID in combination with MMF and oral corticosteroids from randomization onwards.

7.2.2 Dosing Guidelines

7.2.2.1 Orelvo/Placebo – Study Treatment

Study treatment will be taken BID with water on an empty stomach as close to a 12 hour schedule as possible, and with a minimum of 8 hours between doses. If the subject misses a dose of study treatment by less than 4 hours from the anticipated dosing time, the missed dose will be taken immediately. The next dose will be taken at the originally scheduled time. If a missed dose of study treatment is greater than 4 hours from the expected dosing time, the subject will skip the dose and take the next dose at the originally scheduled time. The variation in dosing will be recorded in the eCRFs. The dose/doses of study treatment may be held at the discretion of the Investigator. Subjects must avoid consumption of grapefruit or grapefruit-containing juice (e.g., pomelo) for the duration of their participation in the study.

Possible dose adjustments: If GI or other disturbances occur with study treatment, then study treatment dosing may be reduced or interrupted, and/or appropriate treatment may be initiated (e.g., addition of a proton pump inhibitor (see Appendix 5) and Section 7.6, Orelvo/Placebo Dose Modification).

All unused study treatments (and any empty containers) dispensed to the subject will be returned at each study visit for capsule counts to check compliance. The Investigator will count the returned study treatment and this information will be used to assess subject compliance.

This study treatment count must be documented in the eCRF and source documentation.

7.2.2.2 Corticosteroids

All subjects who weigh ≥45 kg should receive 0.5 g IV methylprednisolone on both Day 1 and Day 2 (a total of 1 g), before oral corticosteroid therapy is started on Day 3. All subjects who weigh <45 kg should receive 0.25 g IV methylprednisolone on both Day 1 and Day 2 (a total of 0.5 g). When subjects are receiving IV methylprednisolone, they should not receive oral corticosteroids on the same day.

If it is considered to be in the subject's best interest, IV methylprednisolone treatment may be started during the screening period, but no more than 1 g in total may be administered for the

screening period and Day 1 and/or Day 2 combined (0.5 g in subjects who weigh <45 kg). Subjects receiving IV methylprednisolone in the 3 months prior to screening must be discussed with the Medical Monitor prior to initiating further IV methylprednisolone. Also, IV corticosteroid therapy to be administered during screening must be discussed with the Medical Monitor in advance. If IV corticosteroid therapy is administered by the site during screening, the dose administered on Day 1 and/or Day 2 will be 1 g minus the dose administered during screening. The maximum daily dose of methylprednisolone administered on Day 1 and/or Day 2 is 0.5 g. See below for examples:

- Example 1: If a 0.6 g dose of IV methylprednisolone is administered during screening, then (1 – 0.6) = 0.4 g IV methylprednisolone will be administered on Day 1, followed by the oral steroid dosing schedule in Table 1, beginning on Day 2 or 3.

- Example 2: If the dose administered during screening is 0.3 g, then the total residual dose required is (1 – 0.3) = 0.7 g. Because 0.7 g is greater than the maximum daily dose allowed, 0.35 g will be administered on Day 1 and 0.35 g on Day 2, followed by the oral steroid dosing schedule in Table 1, beginning on Day 3. If IV methylprednisolone therapy is administered in the 2 weeks prior to the start of screening then the subject is excluded from the study (see Section 7.8.1, Prohibited Medications), unless approved by the Medical Monitor.

- Example 3: In a 40 kg subject, if a 0.3 g dose of IV methylprednisolone is administered during screening then (0.5 – 0.3) = 0.2 g IV methylprednisolone will be administered on Day 1, followed by the oral steroid dosing schedule in Table 1, beginning on Day 2 or 3.

If at screening the Investigator determines a subject requires IV corticosteroid therapy, every effort should be made to collect both morning urine specimens (for UPCR determination) before initiation of the IV steroids. If this cannot be done, the Medical Monitor should be contacted in advance of the therapy (see Section 9.2.1, Screening Visit Procedures).

In the case of the full 1 g IV methylprednisolone being administered prior to randomization (or 0.5 g in a subject <45 kg), it is acceptable for oral prednisone as per dosing schedule to be administered on Day 1.

The starting dose of oral prednisone will be 20 mg/day for subjects <45 kg and 25 mg/day for subjects ≥45 kg. The dose will be reduced according to the tapering schedule below, see Table 1. Refer to Appendix 4 for a conversion table of various formulations of steroids.

Table 1 Dosing Schedule for IV Methylprednisolone and Daily Oral Prednisone (mg)

	Subjects <45 kg	Subjects ≥45 kg	In Case of Prior IV Steroids During Screening (Pre-randomization)
Weeks 1-2[1]			
Days 1-2[2]	0.25 g (IV)	0.5 g (IV)	1 g minus prior IV steroids mg or (0.5 g minus prior IV steroids mg for subjects who weigh <45 kg)[3]
Days 3-13	20 mg (oral)	25 mg (oral)	
Week 2 (Day 14)	15 mg (oral)	20 mg (oral)	
Week 4 (Day 28)	10 mg (oral)	15 mg (oral)	
Week 6 (Day 42)[4]	10 mg (oral)	10 mg (oral)	
Week 8 (Day 56)	5 mg (oral)	5 mg (oral)	
Week 12 (Day 84)	5 mg (oral)	5 mg (oral)	
Week 16 (Day 112)	2.5 mg (oral)	2.5 mg (oral)	

1 Day 0-13: Oral steroids dosed according to subject weight and then tapered beginning at Day 14.
2 Oral corticosteroids may be commenced on Days 1 or 2 if corticosteroids are administered during screening.
3 It is recognized that dosing with IV methylprednisolone as described in Section 7 2 2 2, Corticosteroids may not be in the subject's best interest if they have already received therapy within the 3 months prior to screening. In this case, the Investigator may be permitted to omit the administration of further IV methylprednisolone but only after discussion with the Medical Monitor.
4 Week 6 is not a scheduled study visit, a phone call can be performed to decide further tapering for subjects.

Notes: Oral prednisone taper should be done within ±3 days of specified timeframe. When clinically indicated, subjects are allowed to be completely titrated off of oral corticosteroids.
Abbreviation: IV = Intravenous.

Note that at each visit or during interim phone calls, the corticosteroid dose to be achieved is shown. The timing of the titration to that dose is at the discretion of the Investigator. For example, the Week 6 administration of steroids in a 43 kg subject should be 10 mg daily. The Investigator may reduce it at Week 7 to 7.5 mg until 5 mg is prescribed at Week 8.

When clinically indicated, subjects are allowed to be completely titrated off of oral corticosteroids.

Subjects with a lack of response are allowed one 4-week interval without dose reduction or 1 dose escalation to the previous dose for 2 weeks at any time during the study. Lack of response is defined as no or minimal change in UPCR per Investigator judgment over 3 visits or deterioration in UPCR not meeting the criteria for withdrawal. All deviations from the prescribed dosing schedule in Table 1 above must be discussed with the Medical Monitor and documented in the source notes and eCRF.

7.2.2.3 Mycophenolate Mofetil (Background Therapy)

Subjects receiving MMF prior to randomization will continue without interruption.

- Subjects must be counselled on the risk of pregnancy while taking MMF and the need for adequate contraceptive precautions (see Section 5.4, Adequate/Effective Contraception).

- Subjects on AZA or mycophenolate sodium at screening must switch to MMF at baseline (Day 1).

- For subjects 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 g/day for the first week, increasing to 1 g BID for a total daily dose of 2 g/day for the second and subsequent weeks (i.e., beginning on Day 8).

- Complete blood count must be performed locally at Weeks 1 and 3 in subjects not already taking MMF at screening (unscheduled visit or not).

All subjects will take MMF BID (morning and evening), before meals (i.e., on an empty stomach), with a glass of water. If a dose is missed, the subject should take the next correct dose rather than "doubling up" at the next dosing time point. A stable dose of MMF will be maintained throughout the study. Dose changes or interruptions are permitted for clearly documented safety reasons only.

- Approval by the Medical Monitor is required for subjects taking a dose other than 2 g/day MMF from randomization onwards (e.g., total daily dose of 1 or 3 g/day).

- If GI disturbance or other side-effects occur with MMF, the 1 g BID dosing may be changed to 500 mg four times daily.

- If a subject has an ANC <1,500/mm^3 at any study visit, the dose of MMF should be decreased or interrupted. If a subject has an ANC <1,000/mm^3 at any visit, the dose should be discontinued and only recommenced when the ANC reaches 1,500/mm^3. If the subject has a dose interruption of MMF of >14 days, then permanent discontinuation of MMF, therefore the study, should be considered after discussion with the Medical Monitor.

- If deemed necessary by the Investigator on account of leukopenia or other adverse effect, or if the subject weighs 50 kg or less, the dose of MMF may be decreased to a minimum of 500 mg BID.

7.3 Package and Labeling

All study treatments provided by Aurinia will be packaged and labeled for Aurinia by appropriately qualified vendors according to all applicable local and country regulatory

requirements. All packaging and labeling operations will be performed according to GMP and Good Clinical Practice (GCP).

Study-treatment wallets provided to sites and to subjects will be labeled in the appropriate local language, according to local regulatory requirements.

Wallet label information will be appropriately documented in the Drug Accountability Form after the container has been dispensed to the subject.

7.4 Study Treatment Allocation

For purposes of randomization, each eligible subject will be assigned to 1 of the 2 treatment groups in a 1:1 ratio using IWRS. The randomization will be central-based and stratified by biopsy class (Class V only versus Others) and by prior MMF use at time of the Screening Visit. Randomization will additionally be blocked by region.

7.5 Site Supply, Storage, Accountability

7.5.1 Site Supply

Once a site has been approved for study initiation, the site will be supplied with an initial stock of study treatment. The need for study treatment resupply will be assessed on a regular basis taking into account the number of subjects enrolled at the site.

7.5.2 Storage

Orelvo softgel capsules and matching placebo capsules will be supplied in cartons containing 168 capsules in 4 wallets of 42 capsules each.

The Investigator must ensure the availability of proper storage conditions. All study treatment supplies provided for this study will be stored in a secure area with restricted access at the study site. The capsules must be stored at a controlled room temperature between 15 and 30°C (59-86°F). The Investigator must document and inform the Site Monitor about temperature deviations outside the acceptable range. Subjects will be instructed to store the study treatment at room temperature between 15 and 30°C (59-86°F).

Each site should have a thermometer that records minimum and maximum temperatures daily. Maintenance of a temperature log is mandatory. The log should be updated by site personnel during normal working hours. This log must be available for review by the Site Monitor during on-site monitoring visits.

7.5.3 Accountability

The Investigator at each site is responsible for study treatment supplies. The Investigator will ensure that adequate records of the receipt, dispensing, and return of the study treatment are

kept and that the study treatment is used only for subjects enrolled in the study. All data regarding the study treatment must be recorded on the relevant forms provided.

Each study site will maintain a drug inventory/dispensing record for all drugs dispensed and returned. At the end of the study, 1 copy of the drug inventory/dispensing record should be sent to Aurinia for the central study file. The original will be kept in the site files.

After completion of the study, or if it is prematurely terminated, all unused materials will be returned to Aurinia. The decision to destroy study treatment at a site must be made by Aurinia. If the study treatment is destroyed at a site, the Investigator must receive Aurinia approval of the process and forward the certificate of destruction to Aurinia.

Records of IV methylprednisolone, oral corticosteroids, and MMF must be maintained (prescribed dose, dose adjustments and reasons) in the source notes and must be transcribed into the eCRF.

7.6 Orelvo/Placebo Dose Modification

Dose modifications for background therapy (MMF and corticosteroids) are detailed in Section 7.2, Drug Dosage and Administration.

7.6.1 Deterioration in Renal Function

Serum creatinine and eGFR utilizing the CKD-EPI formula will be used for the assessment of renal function at every visit (Visits 1-15 and unscheduled visit(s)). Subjects will have a minimum of 2 eGFR measurements conducted prior to dosing at Visit 2. The lowest of the pre-dose eGFR assessments will be used as the marker of baseline renal function.

It is recognized that eGFR may be unreliable at higher values (>100 mL/min/1.73 m^2). Lupus nephritis subjects with nephrotic range proteinuria frequently have wide fluctuations in serum creatinine (and therefore eGFR) which are not representative of true renal dysfunction. Chronic kidney disease is defined as eGFR <60 mL/min/1.73 m^2 for ≥3 months [20], with or without kidney damage.

7.6.1.1 Decrease in eGFR >30% and eGFR <60 mL/min/1.73 m^2

During the treatment period, any subject experiencing a >30% decrease in eGFR from baseline to <60 mL/min/1.73 m^2, will have study treatment interrupted until a repeat test can be performed (unscheduled visit to be completed). If the decrease is confirmed and not due to potential contributing factors (e.g., high baseline eGFR, the addition or modification of non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), a concurrent state of dehydration, overdosing with study treatment, lupus renal flare, etc.), the case should be discussed with the

Medical Monitor, the study treatment should be withheld, and eGFR retested within 48 hours. If the eGFR decrease is not confirmed, the study treatment can be restarted at 2 capsules BID and increased as tolerated with discussion with the Medical Monitor.

7.6.1.2 Decrease in eGFR ≤30% and eGFR <60 mL/min/1.73 m^2

During the treatment period, any subject having a ≤30% reduction in eGFR to <60 mL/min/1.73 m^2, should have the influence of potential contributing factors (as described in Section 7.6.1.1, Decrease in eGFR >30% and eGFR <60 mL/min/1.73 m^2) ruled out and appropriate corrective action taken. Any subject having a >20-≤30% reduction compared to baseline in eGFR to <60 mL/min/1.73 m^2 will have a confirmation measurement done within approximately 2 weeks (at a planned study visit, if any, or an unscheduled visit is to be completed). The subjects will be managed in the most medically appropriate manner in consultation with the Medical Monitor. The management of the decrease in eGFR may include reduction of dose or temporary interruption.

7.6.1.3 Recovery of eGFR

Subjects experiencing a decrease in eGFR with resultant decrease in dose should be reassessed for recovery of renal function. If the repeated eGFR is >80% of baseline, the dose should be increased by 1 capsule BID and eGFR assessed within 2 weeks.

7.7 Procedures for Overdose

Based on clinical experience with Orelvo, symptomatic treatment of AEs or overdoses is indicated. Treatment for renal dysfunction, hypertension, and infection may include dose reduction or dose discontinuation. Magnesium supplementation may be required for hypomagnesemia. Treatment for GI complaints and biochemical/hematological abnormalities, and all other expected AEs, should be based on symptoms, with care taken to rule out other causes.

7.8 Prohibited Therapy and Concomitant Treatment

Any concomitant treatment given for any reason during the course of the study must be recorded in the eCRF and in the subject's source documents, including dosage, start and stop dates, and reason for use.

Any class of medications not mentioned below and with the potential to interfere with evaluation of the study treatment must be discussed and documented with the Medical Monitor.

7.8.1 Prohibited Medications

The following medications cannot be taking during the study:

- IV corticosteroids within 2 weeks prior to screening (Visit 1) unless approved by the Medical Monitor
- Enteric-coated oral corticosteroids during the study are not allowed. No other use of non-enteric coated oral corticosteroids, other than administration required as per protocol, is allowed
- IV immunoglobulin treatment within 2 weeks prior to screening (Visit 1)
- Cyclophosphamide within 4 weeks prior to screening (Visit 1)
- Cholestyramine or other drugs that may interfere with enterohepatic recirculation of MMF within 4 weeks prior to screening (Visit 1)
- Initiation of new treatment or change in dosage of ARBs and/or ACE inhibitors within 4 weeks prior to randomization (Visit 2)
- CNIs (e.g., cyclosporine and tacrolimus) within 1 month of screening (Visit 1)
- Immunosuppression biologic agents (e.g., abatacept, belimumab, infliximab, adalimumab, etanercept, or rituximab) within 3 months prior to screening (Visit 1)
- Vaccines using live organisms, viral or bacterial
- MMF dose other than 2 g/day without prior discussion with the Medical Monitor
- Concomitant therapy with other immunosuppressants after randomization, other than MMF administered per protocol
- Subjects are allowed to be on AZA or mycophenolate sodium during screening but must switch to MMF at randomization
- Current or planned use of ketoconazole or rifampin
- Concomitant use of other CYP3A4/5 inhibitors and inducers should be discussed with the Medical Monitor

Appendix 8 contains a summary of additional treatment and food restrictions.

7.8.2 Allowed Concomitant Medications

These medications are permitted during the study:

- Topical steroids (e.g., nose, scalp, skin, inhaled)
- Antimalarials should be prescribed when clinically indicated
- Herbal supplements can be used with caution and depending on active ingredients

Treatments which may be used as medically indicated, according to the judgment of the Investigator can be found in Appendix 7. Treatments not included in this list may be acceptable in the study; such treatments should be verified with the Medical Monitor prior to use. A summary of treatment and food restrictions can be found in Appendix 8.

7.9 Increased Blood Pressure

For all subjects, the target systolic pressure is ≤130 mmHg and the target diastolic pressure is ≤80 mmHg. Investigators should use all means possible permitted in the protocol to maintain the BP within these limits. If no further adjustment of antihypertensive therapy is possible, the subject should be discussed with the Medical Monitor.

If on any study day, systolic BP is >165 mmHg or diastolic BP is >105 mmHg and is associated with symptoms of hypertension (i.e., persistent headache, altered mental status, shortness of breath, chest pain consistent with angina pectoris, symptoms of heart failure, evidence of renal insufficiency of new onset, evidence of hypertensive retinal injury [hemorrhages, papilledema]), study treatment should be held, the Medical Monitor contacted, and the subject treated as per Investigator local practices and best judgment. The subject will continue with all study visits per the Schedule of Events. Study treatment must not be reintroduced without prior discussion with the Medical Monitor.

8. RISKS/PRECAUTIONS

No evidence available at the time of the completion of this study protocol indicated that special warnings or precautions are required, other than those noted in the IB.

If additional special warnings or precautions become apparent before study completion, Aurinia will notify the Investigator at each site.

9. STUDY PROCEDURES

9.1 Description of Study Assessments

9.1.1 Laboratory Assessments

Analysis of all samples for hematology, chemistry, hepatic function, lipid profiles, and urinalysis will be performed at a central laboratory using standard validated methods (see the laboratory manual). All study data analyses involving laboratory values will be based on results from the central laboratory.

The UPCR will be calculated both from the first morning void and from standard urinalysis results. If the first morning void is for some reason not available, then standard urinalysis from a 24-hour urine collection may be substituted as an exception but only after agreement is reached with the Medical Monitor.

Blood and urine samples for the following efficacy and safety assessments (See Table 2) will be drawn in accordance with the Schedule of Events.

Table 2 Review of Laboratory Assessments

Test Type	Test Parameters	Collection at Visits
Hematology	Complete blood count (CBC)	All except Day 2
	Hematocrit	
	Hemoglobin	
	Mean corpuscular hemoglobin (MCH)	
	Mean corpuscular hemoglobin concentration (MCHC)	
	Mean corpuscular volume (MCV)	
	Platelet count	
	Red blood cells (RBC)	
	Red blood cell morphology	
	White blood cells (WBC)	
	Differential (absolute and %)	All except Day 2
	Bands	
	Basophils	
	Eosinophils	
	Lymphocytes	
	Monocytes	
	Neutrophils	
	Erythrocyte sedimentation rate	Day 1, Week 24, and Week 52

Table 2 Review of Laboratory Assessments (Cont'd)

Test Type	Test Parameters	Collection at Visits
Coagulation	Coagulation	Screening
	Activated partial thromboplastin time (aPTT)	
	Prothrombin time (PT)	
	Partial thromboplastin time (PTT)	
Blood Chemistry	Alanine aminotransferase (ALT)	All except Day 2
	Albumin	
	Alkaline phosphatase (ALP)	
	Aspartate aminotransferase (AST)	
	Bicarbonate	
	Bilirubin (direct and total)	
	Blood urea nitrogen (BUN)	
	Calcium	
	Chloride	
	Cholesterol (total, HDL, and LDL)	Day 1, Week 24, and Week 52
	Creatine kinase	Day 1, Week 24,and Week 52
	Creatinine	
	Gamma-glutamyl transferase (GGT)	
	Glucose	
	Glycosolated hemoglobin (HbA1c)	Day 1, Week 24, and Week 52
	Lactic dehydrogenase (LDH)	
	Magnesium	
	Phosphorous, inorganic	Day 1, Week 24, and Week 52
	Potassium	
	Protein, total	
	Sodium	
	Triglycerides	
	c-Reactive Protein	Screening, Week 24, and Week 52
Urinalysis	Complete urinalysis (to include urine protein, creatinine, blood, urine microscopy). First morning void will be performed to analyze urine protein/creatinine ratio. A 24-hour UPCR may be substituted for FMV at entry (or endpoint) if required.	All except Day 2
Pregnancy Test	A serum pregnancy test will be performed for females of childbearing potential. Urine pregnancy tests will be done using a dipstick.	Screening and Weeks 24 and 52 (Serum) All other applicable visits (Urine)

Table 2 Review of Laboratory Assessments (Cont'd)

Test Type	Test Parameters	Collection at Visits
Lupus Markers	Anti-double-stranded DNA (anti-dsDNA) antibodies	Screening, Week 24, and Week 52
	Anti-nuclear antibodies (ANA)	
	Serum	
	Complement 3	
	Complement 4	
	Antiphospholipid antibodies	
	Anticardiolipin antibodies	
	Lupus anticoagulant test	
Serology	Cytomegalovirus	Screening
	Hepatitis A, B, and C	
	Hepatitis B surface antigen (HBsAg)	
Special Tests	Estimated glomerular filtration rate (eGFR)	All except Day 2

Notes: FMV = first morning void; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; UPCR = urine protein creatinine ratio.
Baseline renal function will be the minimum value of any and all eGFR values taken during the screening period and at baseline prior to administration of drug (a minimum of the screen and baseline (pre-dose) values. The central lab will need to report a baseline value for the analysis.

The total amount of blood that will be collected during the study from an individual subject is approximately 300 mL over 56 weeks.

For details on whether laboratory abnormalities should be reported as AEs and on the follow-up required in such cases, see Section 10.2.5, Clinical Laboratory Evaluations.

9.1.1.1 Evaluation of Biomarkers

Samples for biomarker assessments will be obtained in blood / urine and stored (frozen) for future analysis for subjects who consent to have their leftover samples retained.

9.1.2 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Events.

The physical examination will include a review of SLE-related manifestations which will also be recorded. A complete physical examination will be conducted at screening and an abbreviated physical will be performed at all other visits as per the Schedule of Events. The abbreviated examination will consist of checking the normality or abnormality of the following body systems: general appearance, cardiovascular system, and pulmonary system. Any abnormalities will be recorded in the eCRF and reported as an AE. Because the investigational

medication is an immunosuppressant, physical examination will include clinical examination for tumors.

Subject weight will also be recorded at each physical examination; however, height will only be recorded at the screening (Visit 1).

9.1.3 Vital Signs

The following vital signs will be measured in accordance with the Schedule of Events:

- Resting BP (systolic and diastolic)
- Resting HR
- Body temperature (°C or °F)

To avoid variability, the same method of obtaining body temperature should be used throughout the study.

9.1.3.1 Blood Pressure Management

Blood pressure and HR will be measured with the subject in a sitting position after 5 minutes of rest. The procedure for standardized measurement of BP is detailed in Appendix 2.

If the BP measure is confirmed to be >130/80 mmHg (i.e., by the mean of the second and third repeats of 3 readings), the subject's BP will be managed per local practice. If the BP remains uncontrolled with the maximal doses of first and second-line antihypertensive therapies referenced in Appendix 1, then the Investigator should contact the Medical Monitor to consider dose adjustment of the study treatment. See Section 7.9, Increased Blood Pressure for management of increased BP.

9.1.4 Standard 12-lead Electrocardiogram

The electrocardiogram (ECG) will be a standard 12-lead tracing performed at the investigational site, assessed by a qualified physician at the investigational site, and retained as a source document. Any abnormalities will be recorded in the eCRF. Electrocardiograms will be recorded after the subject has been in a resting, supine position for at least 5 minutes. Abnormal ECG tracings can be reviewed by the Medical Monitor. Significant abnormalities, including findings that may prompt discontinuation of study treatment, must be discussed with the Medical Monitor.

Electrocardiograms will be measured at screening, Week 12, Week 24, and Week 52.

9.1.4.1 Procedures to Manage a Treatment-Emergent Increase in QTc

In the event that a subject has a QTcF value exceeding 500 msec, or an increase >60 msec from baseline, the Medical Monitor must be informed. The subject will be asked to return for an unscheduled visit within 24 hours and the ECG will be repeated (confirmed), in triplicate (i.e., three 10-second ECGs in rapid succession within 1 minute). If the repeat measurements confirm that the QTcF is >500 msec or >60 msec from baseline, the subject will be withdrawn from treatment with the study treatment and followed until the QTcF value either returns to baseline (or as appropriate) or until, in the judgment of the Investigator, further evaluation is not clinically indicated.

If study treatment is discontinued, the subject should continue in the study for all remaining scheduled study visits.

9.1.5 Lupus Disease Activity Assessments

The SELENA-SLEDAI assesses disease activity within the last 10 days. Twenty-four items are scored for 9 organ systems, and summed to a maximum of 105 points. A score of 6 is considered clinically significant. See Appendix 6.

Assessments for SELENA-SLEDAI will be conducted at baseline, Week 24, and Week 52.

9.1.6 Orelvo Pharmacokinetics

Blood samples will be taken at Weeks 24 and 52. PK samples will be drawn prior to study treatment dosing (trough sample), and at 2 hours post-dose. These samples will be analyzed for Orelvo. Should a subject experience an SAE, require a dose modification or be withdrawn from treatment, a blood PK sample will be taken (with a trough sample preferred) for later determination of drug level. If a subject has discontinued from study drug treatment, further PK samples are not required.

9.2 Schedule of Assessments

A detailed schedule of assessments (including all protocol-required assessments, visits, and visit windows) is located on the Schedule of Events. No study related assessments will be performed (including changes to current medications to meet study eligibility) until the subject has provided signed and dated informed consent. Every effort will be made to keep the subject within the requested visit schedule. If a subject is seen outside of the visit window listed on the Schedule of Events, the reason must be clearly documented in the source notes. The Investigator (or designee) should contact Aurinia for assistance with getting the subject's schedule back on track in order to avoid large variances in treatment exposure or to avoid delaying overall study timelines.

9.2.1 Screening Visit Procedures

The screening visit (Visit 1) will take place within 30 days prior to Visit 2/baseline (Day 1). Screening will include provision of informed consent, physical examination including weight, and height, medical history (including SLE and LN history), vital signs measurements, 12-lead ECG, and review of prior and concomitant medications and entry criteria. Any AEs which occur after informed consent will be recorded. Urine samples will be collected for urinalysis and urine microscopy; first morning void urine samples (for determination of UPCR) will be collected on 2 days during the screening period and must be returned and the results evaluated prior to Visit 2. An average of the 2 screening UPCRs will be used as a marker of baseline urine protein excretion. Baseline proteinuria level is determined by a mean of 2 first morning void urine samples taken during the screening period. The lowest of pre-dose eGFR assessments will be used as the marker of baseline renal function. It is recommended that in the event that IV corticosteroids are administered during screening, the 2 first morning urine voids are to be collected prior to administration of the corticosteroids (see Section 7.2.2.2, Corticosteroids). In the case where this is not possible, then the marker of baseline urine protein excretion will be based upon the Visit 1 UPCR collection only. This must be discussed with the Medical Monitor prior to enrollment. Please note that the results of the 24-hour urine collection will have to be available prior to the Baseline Visit.

Blood samples will be drawn according to Table 2.

If the subject is from an area where TB is endemic or whose history suggests an increased personal risk, e.g., from contact with people with TB or travel to areas with endemic TB, the subject will be carefully evaluated for latent or active TB.

Women of childbearing potential should have a negative serum pregnancy test result before randomization. Study treatment cannot be initiated by the physician until a report of a serum negative pregnancy test has been obtained.

If a subject has not met the requirements in Inclusion Criteria #4 due to not having kidney biopsy result within the required time frame, a kidney biopsy can be performed as per local procedures, after signing the study consent, provided the results can be obtained and reviewed prior to randomization.

9.2.2 Treatment Procedures

Only subjects who satisfy all of the inclusion and exclusion criteria will be eligible for randomization and study treatment.

Subjects will be fasting for at least 8 hours on the day of randomization and all visit procedures must occur prior to the first dose of study treatment on Day 1. The MMF dose required per

protocol and IV methylprednisone (or oral corticosteroids) will also be administered at baseline before the first dose of Orelvo.

Subjects will complete all assessments per the Schedule of Events at Day 1, Day 2, and at Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48. IWRS will be accessed to assign study treatment to subjects at appropriate visits.

Adverse events and concomitant medication will be recorded prior to the conduct of other study assessments at each visit.

Assessments at visits during the treatment period include:

- SF-36 and LupusPRO HRQoL will be answered by the subject, as first study procedure, at Baseline, Week 12 and Week 24
- Physical examination including weight
- Vital signs
- ECG at Week 12 and Week 24
- Blood and urine sample collection for analysis at central laboratory
- First morning void urine sample collection, except before Day 1 and Day 2 Visits
- 24-hour urine collection at Week 24 (**IMPORTANT**: 24-hour urine collection will have to begin 2 days prior Week 24 visit in order not to coincide with the first morning void sampling due on the day of this visit)
- Pregnancy testing (serum: Week 24; urine: Day 1 and Weeks 2, 4, 8, 12, 16, 20, 30, 36, 42, and 48) and immunology
- AEs
- Concomitant medication
- SELENA-SLEDAI will be evaluated at Baseline and Week 24
- Dispense study treatment – including study treatment and background therapy
- Returned capsule count and drug accountability

- Information for the healthcare resource utilization assessment will be collected and recorded at Day 1 and Week 52

9.2.3 End of Study (or Early Discontinuation) Procedures

On completion of treatment at Week 52 or earlier if subject is discontinued/withdrawn early, all assessments for Visit 15 (end of study/early termination) will be completed per the Schedule of Events. See also Section 5.5, Withdrawal of Subjects, for further information on withdrawal procedures and criteria.

The following assessments for the end of study visit will be performed:

- SF-36 and LupusPro HRQoL
- Abbreviated physical examination (including body weight)
- Vital signs
- Standard 12-lead ECG
- Blood sample collection for analysis at central laboratory
- Serum pregnancy testing
- First morning void
- 24-hour urine sample collection (**IMPORTANT**: 24-hour urine collection will have to begin 2 days prior to Week 52 visit in order not to coincide with the first morning void sampling due on the day of this visit)
- Concomitant medication
- AEs
- SELENA-SLEDAI
- Returned capsule count and drug accountability
- Confirmation of completion/discontinuation using IWRS
- Information for the healthcare resource utilization assessment will be collected and recorded

9.2.4 Follow-up Procedures

All subjects who complete the study but do not participate in the continuation study or discontinue study treatment before Week 52 will be followed up 4 weeks (±10 days) after their last study treatment dose to collect any new AEs and concomitant medications. This visit (Visit 16) will be conducted as an in-clinic visit.

Assessments for the follow-up visit are as follows:

- Vital signs
- Blood sample collection for analysis at central laboratory (eGFR)
- First morning void urine sample collection
- Concomitant medication
- AEs
- Confirmation of completed follow-up visit using IWRS

9.2.5 Unscheduled Visit

Unscheduled visits may be performed during the course of the study for safety reasons. An unscheduled visit is required 2 weeks after dose reduction at any time during the study. Only the data relevant to the purpose of the visit will be collected in the source documents and eCRF. An unscheduled visit is requested in the following cases:

- QTcF value exceeding 500 msec, or an increase >60 msec from baseline, where the ECG will be repeated (confirmed) at an unscheduled visit
- Systolic BP is ≥165 mmHg or diastolic BP is ≥105 mmHg, or confirmed systolic BP >130 mmHg or a diastolic BP >80 mmHg
- Decrease in eGFR >30% compared to baseline, or a confirmed decrease in eGFR >20-30% compared to baseline
- Complete blood count must be performed locally at Weeks 1 and 3 in subjects not already taking MMF at the Screening Visit

9.3 Study Specific Assessment Procedures

9.3.1 Health-related Quality of Life Assessments (HRQoL)

9.3.1.1 Short Form Health Survey (SF-36)

The SF-36 HRQoL assessment is a 36-question subject HRQoL questionnaire and is presented in Appendix 9.

9.3.1.2 LupusPRO

The LupusPRO (v1.7) is a 43-question subject HRQoL questionnaire specific for lupus and is presented in Appendix 10.

9.3.2 Healthcare Resource Utilization Assessment

The collection of information on healthcare resource utilization will be collected at the time points specified in the Schedule of Events (Day 1 and Weeks 24 and 52) and documented in the EDC system. This information will be collected via interview of the subject by the study staff and entered into the EDC system. General information collected may include:

- Type of insurance coverage
- Number of visits to ANY health care professionals (HCP), other than study doctor
- Types of HCP visited (specialists versus primary care)
- Time spent on visits
- Diagnostic tests performed
- Time spent by caregivers assisting patient with HCP visits (can ask general question if subject required a family member or other person to assist them to attend the visit)
- Prescriptions issued, filled
- Community services used

10. EVALUATION, RECORDING AND REPORTING OF AEs AND SAEs

10.1 Definitions

10.1.1 Adverse Event

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

10.1.2 Adverse Drug Reaction

In the pre-approval clinical experience with a new medical product or its new usages, particularly as the therapeutic dose(s) may not be established, all unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

10.1.3 Serious Adverse Event

An SAE (experience) or reaction is an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Results in death (Note: death is an outcome, not an event)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important event or reaction

The definitions and reporting requirements of International Council for Harmonisation (ICH) Guidelines for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2 will be adhered to.

Medical and scientific judgment must 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These will also usually be considered serious.

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 subject's source documents before the subject signed the informed consent form (ICF). A kidney biopsy performed as part of the study to verify eligibility 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.

10.1.4 Suspected Unexpected Serious Adverse Reaction

Any ADR that is both serious and unexpected (per the IB) that, based on the opinion of the Investigator or Aurinia, is felt to have a reasonable suspected causal relationship to a medicinal product is a suspected unexpected serious adverse reaction.

10.2 Adverse Event Descriptors

10.2.1 Intensity/Severity Categorization

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); however the event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

In general, the intensity of a particular AE to be recorded is the worst intensity experienced by the subject during the course of the event. The medical assessment of intensity will be determined by using the following definitions:

Mild: The AE is easily tolerated and does not interfere with usual activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and the subject is unable to work or complete usual activity.

10.2.2 Causal Relationship Categorization

An Investigator who is qualified in medicine must make the determination of relationship to the study treatment for each AE and SAE. The Investigator must decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study treatment. If there is no valid reason for suggesting a relationship, then the AE/SAE must be classified as not related. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a cause-and-effect relationship between the study treatment and the occurrence of the AE/SAE, then the AE/SAE will be considered related. For SAEs, the Investigator must provide a brief comment explaining the rationale of his/her assessment of causal relationship on the SAE reporting form.

The following additional guidance may be helpful:

Term	Relationship	Definition
Related	Yes	The temporal relationship of the clinical event to study drug administration indicates a causal relationship, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
Not related	No	The temporal relationship of the clinical event to study drug administration does not indicate a causal relationship, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

If the causal relationship between an AE/SAE and the study treatment is determined to be "related", the event will be considered to be related to study treatment for the purposes of expedited regulatory reporting. In circumstances where the Investigator has not yet provided his/her assessment about the relationship, the event will be considered as "related" and qualify for expedited regulatory reporting.

10.2.3 Outcome Categorization

Outcome may be classified as recovered without sequelae; recovered with sequelae; improved; worsened; ongoing; ongoing at end of study; fatal; or unknown. If the outcome is reported as recovered with sequelae for an SAE, the Investigator should specify the kind of sequelae on the SAE reporting form. SAEs that are ongoing at the time of death will have an outcome of "unknown" recorded. SAEs resulting in a fatal outcome will have an outcome of "fatal" recorded.

10.2.4 Symptoms of the Disease Under Study

Symptoms of the disease under study will not be classed as AEs as long as they are within the normal day-to-day fluctuation of the disease. An explanation of these circumstances must be written in the source documents.

Worsening of the symptoms however, will be recorded as an AE, and clearly marked as worsening or by the subject's worst observed intensity.

10.2.5 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant in the opinion of the Investigator or if, during treatment with the study treatment, a shift of a parameter is observed from a normal value to a pathological value, or a further worsening of an already pathological value.

If, at the end of the treatment phase, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations will be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

If the Investigator considers such an AE as serious it must be reported as an SAE.

10.2.6 Abuse, Misuse, Overdose and Medication Error

All AEs of special interest such as study treatment abuse, misuse, overdose, and medication error have to be documented in the subject's eCRF and source documentation. If any occurrence of abuse, misuse, overdose, or medication errors leads to any event that fulfils any seriousness criteria, the event has to be reported as an SAE.

10.3 Reporting Procedure for AEs, SAEs, and Pregnancy

10.3.1 Adverse Events

All AEs either observed by the Investigator or one of his/her medical collaborators, or reported by the subject spontaneously, or in response to a direct question, will be noted in the AE section of the subject's eCRF and source documentation. This applies to all AEs regardless of presumed relationship to the study treatment. Adverse events leading to discontinuation of study treatment must be collected.

If any AE is reported, the date of onset, relationship to study treatment, any action taken, date of resolution (or the fact that it is still continuing or has become chronic), outcome, and whether the AE is serious or not, will be recorded. Use of colloquialisms and abbreviations should be avoided. Only 1 AE term should be recorded in the event field on the AE eCRF. Where possible, the Investigator should report a diagnosis rather than signs and symptoms or

abnormal laboratory values. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

The AE reporting period begins at the time the ICF is signed by the subject. The AE reporting period ends at Visit 15 (if the subject participates in the continuation study) or the study follow-up visit (Visit 16), if the subject does not participate in the continuation study. Adverse events persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilization has occurred (or the subject is lost to follow-up and cannot be contacted) and recorded in the source documents. If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc. In circumstances where the Investigator is unable to make contact with the subject, the Investigator must provide a written statement to Aurinia confirming that the subject is lost to follow-up.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be considered AEs.

10.3.2 Serious Adverse Events

All SAEs occurring after the signing of the ICF will be reported to [redacted] within 24 hours of the Investigator, designee, or site staff's knowledge of the event regardless of relationship to study treatment. All SAEs are to be reported on the eCRFs.

In the event that the site experiences a temporary disruption of the EDC system a back-up paper SAE Reporting Form will be available for site staff to complete.

- Site staff will complete the paper SAE report form and e-mail it within 24 hours to the following address: [redacted]
- Only in cases where the email system is unavailable, site staff will send the SAE by fax to: [redacted] (US) and [redacted] (Outside US).

If notification is made via email or fax, site staff must enter the SAE information into the electronic data capture (EDC) system as soon as the system becomes available.

All SAEs, regardless of causality, will be reported from the time the ICF is signed until 30 days following the last study visit or 30 days after last study treatment administration in subjects who withdraw or discontinue prior to study completion. No formal study visit is required but Investigators must report any SAEs that occur during this 30 day period on the eCRF. If the Investigator has not seen the subject at a clinic visit at the end of the reporting period, the Investigator must make reasonable efforts to contact the subject to inquire about SAEs.

All recorded SAEs, regardless of relationship to study treatment, will be followed up until resolution, stabilization, or the subject is lost to follow-up and cannot be contacted. In circumstances where the Investigator is unable to make contact with the subject, the Investigator must provide a written statement to Aurinia confirming that the subject is lost to follow-up.

Any SAE considered to have a causal relationship (i.e., "related") to the study treatment and discovered by the Investigator at any time after the study will be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator. Any safety information that is obtained after the Follow-up Visit (Visit 16) will be documented in the safety database only.

A death occurring during the study or which comes to the attention of the Investigator within 30 days after the last study visit (including the Follow-up Visit) or until 30 days after the last study treatment administration, whichever is longer, whether considered treatment-related or not, must be reported to Aurinia. If the subject died, the SAE report should include the cause of death as the event term and whether or not the death was related to study treatment, as well as the autopsy findings, if available. Preliminary reports will be followed by detailed descriptions which will include copies of hospital case reports, autopsy reports/certificates and other documents when requested and applicable.

Additional follow-up information must be reported in the eCRF within 24 hours of awareness following Investigator (or site) awareness of the information. The Investigator should not delay reporting an SAE in order to obtain additional information. Additional information, when available, should be reported to [redacted] by the reporting procedures described above.

The Investigator is encouraged to discuss with the study Medical Monitor when the issue of seriousness is unclear or questionable.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

The sponsor or its representative will be responsible for determining and, in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

10.3.3 Pregnancy

Pregnancy occurring in a female subject or in the partner of a male subject should be reported to [redacted] within 24 hours of becoming aware of the event using the pregnancy eCRF. The Investigator should counsel the subject, and in the case of a male subject, the subject's partner, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. A female subject must immediately inform the Investigator if she becomes pregnant during the study. Monitoring of the pregnancy in a female subject should continue until conclusion of the pregnancy. In case of a pregnancy in the partner of a male subject, the Investigator should obtain informed consent of the pregnant partner prior to monitoring of the pregnancy.

Women who have a positive pregnancy test during the study will be withdrawn from the study treatment and the procedures for withdrawal will be completed. The Medical Monitor must be contacted immediately to break the blind (if applicable).

All pregnancies, subject or partner of a subject, that occur during the study or come to the attention of the Investigator within 30 days after the last study visit (including the Follow-up Visit) or until 30 days after last study treatment administration, whichever is longer, must be reported to [redacted] by the reporting procedures described above.

The outcome of all such pregnancies (including normal births) should be followed up and documented, even if the subject was withdrawn from the study. Every effort should be made to gather information regarding the pregnancy outcome until 90 days (or otherwise as appropriate) post-partum. It will be the responsibility of Aurinia, together with the appropriate support of the Investigator, to obtain this information.

Complications of pregnancy such as abortion (spontaneous or induced), premature birth, or congenital abnormality are considered SAEs and should be reported following the reporting procedures as outlined in Section 10.3.2, Serious Adverse Events. In the event that the site experiences a temporary disruption of the EDC system, a back-up paper Pregnancy Reporting Form will be available for site staff to complete.

11. CLINICAL ENDPOINTS COMMITTEE

A CEC will be constituted to adjudicate the following renal response (primary efficacy endpoint) parameters for subjects in this study:

- UPCR of ≤0.5 mg/mg, and
- eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20%, and
- Received no rescue medication for LN (see Section 7.8, Prohibited Therapy and Concomitant Treatment), and
- Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52, just prior to the renal response assessment

The CEC will adjudicate renal response by reviewing blinded data. Aurinia will establish a charter document explaining the working procedures and responsibilities of the CEC. All adjudication decisions of the CEC will be appropriately documented.

12. DATA AND SAFETY MONITORING BOARD PROCEDURES

A DSMB will be constituted to protect the safety of study participants. The DSMB will receive blinded eCRF data in the form of tables and listings (prepared by an independent statistician), and review subject status changes and dosing decisions (where appropriate). Where appropriate, the DSMB may receive unblinded data (on a subject level or treatment group level) that should be reviewed in a closed session. The data should include, but is not limited to, demographics, subject enrollment, baseline characteristics, AE data, SAE data (by severity and causality), laboratory data, dose adjustments, protocol adherence, and subject withdrawals. The DSMB will evaluate the progress of the study, assess data quality and timeliness, participant recruitment, accrual and retention, and participant benefit versus risk. In addition the DSMB will monitor external factors relevant to the study, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects, the DSMB will make recommendations to Aurinia concerning continuation, termination, or modifications of the study.

Aurinia will establish a charter document explaining the working procedures and responsibilities of the DSMB. All deliberations and decisions of the DSMB will be appropriately documented.

13. STATISTICAL ANALYSIS

13.1 Statistical Methods

Complete details of the statistical and analytical methods will be provided in a formal Statistical Analysis Plan (SAP), which will be finalized prior to the database lock. A general description of the planned methods is provided below. Any deviation from the SAP will be noted and explained in the clinical study report.

13.2 Sample Size and Power Calculations

The total sample size will be 324 subjects (162 subjects per treatment arm). This is based on the following assumptions:

- A two group continuity corrected Chi square test with a 0.05 two-sided significance level will have 80% power to detect the difference between a placebo response rate of 20.0% and a Orelvo response rate of 34.4% (odds ratio=2.1) when the sample size in each group is 162 (total N=324).
- The effect of withdrawals will be investigated. Subjects withdrawing for any reason will be counted as non-responders in the primary analysis and therefore no adjustment of sample size for withdrawals is necessary.
- The impact of withdrawals on primary endpoint will be investigated with a tipping point analysis.

Table 3 shows the Orelvo response rates required to maintain a minimum 80% power at the planned sample size for given placebo response rates. These response rates all lead to odds ratios of around 2, which is a clinically relevant effect.

Table 3 Orelvo Response Rates Required to Maintain a Minimum 80% Power

Placebo Response Rate	Orelvo Response Rate	Odds Ratio
15%	28.4%	2.25
19%	33.2%	2.12
25%	40%	2.0

Note: Based on the planned sample size of 324 subjects (162 subjects per treatment arm).

13.3 Populations

13.3.1 Intent-to-Treat Set

The intent-to-treat set will be based on intent-to-treat (ITT) principles and will consist of all subjects who are randomized to treatment. This group will be analyzed based on the treatment to which the subject was randomized.

13.3.2 Safety Set

The safety set will consist of all randomized subjects who have taken at least 1 dose of study treatment. The subjects in this group will be analyzed based on the treatment they received. Subjects who receive treatment from more than 1 arm will be assigned to the Orelvo arm.

13.3.3 Per-protocol Set

The per-protocol set will consist of all subjects eligible from the ITT population who do not have any major protocol violations. Major protocol violations will be defined in the statistical analysis plan and fully assessed at the subject level prior to unblinding of the study.

13.4 Background and Demographic Characteristics

Demographic and clinical disease characteristics will be summarized by treatment arm in a descriptive manner but no statistical tests will be performed.

13.5 Study Treatment

Compliance to the study treatment will be determined by dividing the number of softgel capsules taken by the expected number of softgel capsules to be taken (based on prescribed dose) over the subject's participation in the study.

Results will be summarized by means of descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) and frequency tables, by treatment arm.

13.6 Concomitant Therapy

All concomitant medications will be coded by the WHO Anatomical Therapeutic Chemical Drug Reference List classification. The version used will be provided in the clinical study report.

13.7 Efficacy Evaluations

13.7.1 Primary Endpoint

The primary endpoint is the number of subjects showing renal response at 52 weeks. Renal response at Week 52 will be adjudicated by the CEC based on the following parameters:

- UPCR of ≤0.5 mg/mg, and
- eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20%, and
- Received no rescue medication for LN (see Section 7.8, Prohibited Therapy and Concomitant Treatment), and

- Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52, just prior to the renal response assessment

Subjects who withdraw from the study prior to the Week 52 assessment will be defined as non-responders.

13.7.2 Secondary Endpoints

13.7.2.1 Key Secondary Endpoints

- Time to UPCR of ≤0.5 mg/mg
- Partial renal response as defined by 50% reduction from baseline UPCR at Weeks 24 and 52
- Time to 50% reduction in UPCR from baseline
- Renal response at Week 52 (based on definition of primary endpoint)
- Duration of UPCR ≤0.5 mg/mg
- Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each timepoint

13.7.2.2 Other Secondary Endpoints

- Change from baseline in UPCR at each time point
- Change from baseline in serum creatinine, urine protein, and eGFR
- Change from screening in immunology parameters (C3, C4, and dsDNA) at Weeks 24 and 52
- Renal response with low-dose steroids (defined as renal response in the presence of corticosteroids of ≤2.5 mg/day between Weeks 16 to 24 and Weeks 44 to 52)
- Change from baseline in HRQoL at Weeks 12, 24, and 52
- Health Resource Utilization at Weeks 24 and 52
- Change from baseline in the SELENA-SLEDAI Index score at Weeks 24 and 52

13.8 Statistical and Analytical Methods

13.8.1 Primary Efficacy Analysis

The primary efficacy endpoint is the renal response at Week 52 (Section 13.7.1, Primary Endpoint).

The study null hypothesis H_0 and alternative hypothesis H_1 are as follows:

H_0: There is no difference in renal response between Orelvo and placebo.

H_1: There is a difference in renal response between Orelvo and placebo.

The null hypothesis H_0 will be rejected in favor of H_1 if there is evidence at the 5% significance level using a 2-sided test.

The primary efficacy analysis will be conducted on the ITT set using logistic regression with terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline. The results being expressed as an odds ratio (and associated two-sided 95% CI) for Orelvo compared to placebo. Odds ratios greater than unity show the odds of response are greater for Orelvo than for placebo and therefore indicate a benefit of the Orelvo treatment arm.

13.8.2 Sensitivity Analyses

The following sensitivity analyses will be performed:

- Renal response at Week 52 will be analyzed using a logistic regression including only a term for treatment. This analysis will be performed on the ITT set.
- The analysis described in Section 13.8.1, Primary Efficacy Analysis will be repeated for the per protocol analysis set.
- The impact of withdrawals on primary endpoint will be investigated with a tipping point analysis.

13.8.3 Secondary Efficacy Analysis

All the secondary efficacy analyses will be performed on the ITT set.

13.8.3.1 Response Endpoints

The following secondary endpoints will be analyzed using logistic regression as outlined in Section 13.8.1, Primary Efficacy Analysis. These analyses will be conducted on the ITT population and will incorporate baseline variables within the model as appropriate.

- Renal response at Week 52 (based on definition of primary endpoint)

- Partial renal response as defined by 50% reduction from baseline in UPCR at Weeks 24 and 52

- Renal response with low-dose steroids (defined as renal response in the presence of corticosteroids of ≤2.5 mg between Weeks 16 to 24 and Weeks 44 to 52)

13.8.3.2 Time to Endpoints

The following secondary endpoints: time to renal response, time to partial renal response, and duration of UPCR ≤0.5 mg/mg will be analyzed by comparing the survivor function between treatment arms. It will be estimated using Kaplan-Meier methodology and will be presented as a plot showing a line for each treatment group. Median time-to-event along with two-sided confidence intervals will be displayed.

Cox's proportional hazards model will be performed to assess the significance of the differences between treatment arms. The model will include terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline. Estimates of the treatment effects will be expressed as hazard ratios (and associated 95% CI) for Orelvo relative to placebo. Hazard ratios greater than unity show the hazard to be greater for Orelvo than for placebo and therefore indicate that the events in question generally occur earlier on active Orelvo.

The log-rank test and Cox's proportional hazards model assume that the hazard ratio is constant over time. This assumption will be checked graphically by plotting log-log survivor functions for the treatment groups. It should be noted that modest deviations from the proportionality assumption generally will not invalidate inference.

13.8.3.3 Change from Baseline Endpoints

The following secondary endpoints will be analyzed using a Mixed Effect Model Repeated Measures analysis with treatment arm, visit, treatment by visit interaction, biopsy class, and MMF use at baseline included as a covariate in the model. Results will be expressed as differences between treatment arms (along with the associated 95% CI).

- Change from baseline in UPCR at each visit

- Change from baseline in serum creatinine, urine protein, and eGFR at each visit

- Change from screening in immunology parameters (C3, C4, and anti-dsDNA) at Weeks 24 and 52

- Change from baseline in HRQoL at Weeks 12, 24, and 52

- Change from baseline in the SELENA-SLEDAI score at Weeks 24 and 52

13.8.3.4 Health Resource Utilization

- Health Resource Utilization at Weeks 24 and 52. Key aspects will be summarized by visit and changes over time will be explored.

13.8.4 Multiplicity

An overall type 1 (false-positive) error rate of 5% for the efficacy endpoints will be maintained so that no statistical significance for the secondary efficacy endpoints will be claimed unless the principal analysis of the primary efficacy endpoint using the ITT set is statistically significant at the 5% level. The Hochberg step-up method will be used to adjust for multiple comparisons amongst key secondary endpoints and maintain the overall type 1 error rate [21]. Data from all analyses, regardless of the level of significance, will be presented for review.

13.9 Safety Evaluations

Specific safety endpoints are as follows:

- Biochemical (including liver function tests) and hematological laboratory tests
- AE profile and routine biochemical and hematological safety parameters
- Vital signs (BP, HR, temperature) at specific time points and change from baseline
- Standard 12-lead ECGs change from baseline
- Discontinuations from treatment
- Concomitant medications

Laboratory values, vital signs, and other safety parameters providing numeric data will be summarized by treatment arm, visit, and as change from baseline.

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities, the version of which will be provided in the clinical study report.

Treatment-emergent adverse events will be summarized by treatment arm, system organ class, and preferred term. SAEs, SAEs that led to death, and SAEs/AEs that led to withdrawal will also be summarized and listed.

Only AEs which started on or after the date of first dose of study treatment will be considered TEAEs, though all AEs after informed consent will be recorded. SAEs occurring at any time after informed consent will be summarized. All concomitant medications will be summarized.

Details of these and other analyses will be provided in the SAP.

All study data analyses involving laboratory values will be based on results from the central laboratory.

13.10 Interim Analyses

There are no planned interim analyses.

13.11 Other Evaluations

13.11.1 Pharmacokinetics

Estimates of Orelvo exposure derived from this analysis will be examined for possible relationship to measures of efficacy and safety. Full details will be described in a separate analysis plan.

14. ETHICAL CONDUCT OF THE STUDY

The study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki [21] and the ICH guidelines for GCP [23]. Aurinia will ensure that the study complies with all local, federal, and country regulatory requirements.

The Investigator must ensure the confidentiality of all subjects participating in the study.

All anonymous data remains the property of Aurinia.

14.1 Informed Consent

The ICF used for the study must comply with the Declaration of Helsinki, federal regulations, and ICH guidelines; and must have been approved by the Institutional Review Board (IRB)/Ethics Committee (EC)/Independent Ethics Committee (IEC) prior to use. The Investigator or an authorized associate must explain the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects must be provided sufficient time to consider participation, including discussion with family members prior to signing the ICF. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. After signing the ICF, subjects will be enrolled into the study and assigned a subject identification number that will be used on all subject documentation.

The informed consent can be signed up to 30 days before the screening Visit 1. If more than 30 days elapses between date of consent and the screening Visit 1, the subject should be asked to re-sign and date the consent form to confirm continued interest in study participation.

14.2 Institutional Review Board or EC/IEC

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local IRB/EC/IEC must be submitted by the Investigator for review and approval to the IRB/EC/IEC. The Investigator must also ensure that the IRB/EC/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study per local requirements.

15. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all study-related site source data, study-related documents, and reports will be available, and that the provision of direct access for monitoring and auditing by Aurinia or its designees will be permitted. In addition, the Investigator must ensure that all study-related site source data, study-related documents, and reports will be made available for inspection by the appropriate Regulatory Authority and review by the IRB/EC/IEC.

The Investigator is responsible for notifying Aurinia in advance of an impending regulatory inspection. He/she may request that Aurinia provide support for preparation, if necessary. The Investigator is required to provide updates to Aurinia on the ongoing activities during the inspection, respond to any citations/objectionable findings (i.e., U.S. Food and Drug Administration Form 483) and to share any follow up responses from the Regulatory Authority.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the Study Monitor (source document verification). The Monitor will also review the Investigator's drug accountability records to ensure that the drug supplies are stored and dispensed appropriately. A comprehensive validation program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, Aurinia or its designates may review data as deemed necessary.

16. ADMINISTRATIVE PROCEDURES

16.1 Sponsor's Responsibilities

16.1.1 Study Supplies

Sites will be provided with all supplies required to manage this study. This will include but not be limited to the following:

- Investigator file(s) (for filing of all study related documentation).
- Kits for collection, storage, and transportation of applicable samples required for central laboratories. This will also include all applicable guidelines and contact details.
- Contact list of all relevant study personnel.
- eCRF and completion guidelines (or equivalent electronic data capture system).
- Study reference manual.
- All study forms (e.g., SAE, pregnancy, drug accountability, etc.).

16.1.2 Insurance

Aurinia confirms that it carries liability insurance which protects non-employee physicians or Investigators/study staff against claims for which they may become liable as a result of damages caused by Aurinia products used in clinical studies. Insurance coverage is not extended to damages that the Investigators or third parties may suffer by reason of acts of commission or omission on the part of such Investigators or third parties and that are not in accordance with accepted common medical practices (*lege artis* procedures). Aurinia will reimburse the subject for all study-related injuries provided that the injury does not arise from the subject's misuse of the study treatment or failure to follow the Investigator's instructions.

16.1.3 Study Monitoring

The study will be monitored by representatives of Aurinia (or designee, which may include a contract research organization). If not monitored by Aurinia, documentation of delegation will be described in the Clinical Trial Agreement. It is understood that the responsible Monitor will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements.

It will be the Monitor's responsibility to inspect the eCRFs at regular intervals throughout the study (frequency outlined in a separate procedural document), to verify the adherence to the

protocol and the completeness, consistency, and accuracy of the data being entered on them. The Monitor must have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or his/her deputy) agrees to co-operate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

16.2 Investigator's Responsibilities

16.2.1 Reporting and Recording of Data

All required study data must be entered in the eCRF created for the study. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures, and electronic signatures. Only individuals who are identified on the authorized signature page may enter/correct data in the eCRF. For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries addressed to the Investigator for resolution.

16.2.2 Investigator Training

All Investigators and their study personnel will receive training regarding the study procedures, study treatments, and GCP/regulations specific to the conduct of clinical studies. This training will take place prior to enrollment of the first subject at the study site, and must be documented and filed in the Investigator's Study Site File.

16.2.3 Source Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Subject clinical source documents would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. These are to be separate and distinct from eCRFs. All data for the study must be available in source documentation, including oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.

The Investigator must arrange for the retention of all study documentation (such as eCRFs, research files, and master files) for the duration specified in their respective site contract. The Investigator must keep these documents on file after completion or discontinuation of the study according to local governing guidelines. Archived data may be held electronically, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform Aurinia immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

17. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

17.1 Protocol Waivers, Deviations and Violations

Protocol waivers shall not be permitted.

The Investigator should not implement any deviation from, or changes of the protocol without written agreement from Aurinia and prior documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when change(s) involves only logistical or administrative aspects of the study. If the Investigator must implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior written approval, the implemented deviation or change and the reasons for it should be submitted in a timely manner to Aurinia and to the IRB/IEC as required by applicable local requirements.

The Investigator, or person designated by the Investigator, will document and record the preventative and/or corrective measures for any deviation from the approved protocol.

Accidental deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as minor or major on a case-by-case basis. The criteria describing the deviation(s) and how they will be handled will be documented in the SAP.

Any amendment to the protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the reviewed document prior to administering to study subjects.

17.2 Study Termination

Aurinia reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include, but are not limited to the following: unsatisfactory subject enrollment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

In terminating the study, Aurinia and the Investigator will assure that adequate consideration is given to the protection of the subjects. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

18. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

Aurinia is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [24]. Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by Aurinia before submission for publication. Names of all Investigators participating in the study will be included in the publication.

The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria [25] for authorship. If studies are multicenter, it may be appropriate to assign group authorship.

In addition, certain Aurinia employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee.

19. REFERENCES

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Appendix 1 Drug Therapy for the Treatment of Hypertension

Antihypertensive drug therapy for subjects who either have hypertension at screening or who develop hypertension while on study treatment may include the following:

- Dihydropyridine calcium channel blockers (e.g., amlodipine, nifedipine)
- Alpha-1-adrenergic blocking agents (e.g., doxazosin)
- Alpha-beta-blockers (e.g., carvedilol, labetalol)
- Thiazide diuretics (e.g., chlorthalidone or hydrochlorothiazide)

Excluded Drugs: While the ARBs and ACE inhibitors may also be effective in calcineurin inhibitor-associated hypertension, their dose adjustment or commencement is not permitted in this trial (see Section 7.8.1, Prohibited Medications).

Recommended First and Second Line Therapies for Treatment of Hypertension

Titrate the following according to the timeframe given in the respective drug label:

First Line - select from one of the following:

- Amlodipine, 5 mg daily to achieve BP <140/90 mmHg; titrate to 10 mg daily if satisfactory results not obtained within 2 weeks
- Nifedipine XL, 30 mg daily; titrate to 60 mg and possibly 90 mg daily within 2 weeks
- 12.5 to 25 mg/day of chlorthalidone or hydrochlorothiazide

Second Line - may add from among the following to the first line therapy if a partial response is obtained:

- Labetalol, 100 mg BID; titrate to 200 mg BID, then 300 mg BID

Note: If the BP remains uncontrolled with the above-referenced maximum doses of first and second-line antihypertensive therapies, reduction of study treatment dose may be considered or it may be decided to discontinue study treatment and utilize antihypertensive therapies to achieve control of BP.

If at any time, in the judgment of the treating physician in consultation with the Medical Monitor, the response to treatment is inadequate, the study treatment may be discontinued.

Appendix 2 Measurement of Blood Pressure

1. Whenever possible, BP measurements should be undertaken by the same study site personnel at each clinic visit.

2. Whenever possible, the BP determinations should be undertaken at approximately the same time of day for each study visit and at the same time in relations to prior study treatment ingestion.

3. The measurements should be undertaken prior to blood collection.

4. Prior to measuring BP, the study subject should be seated in a quiet room for at least 5 minutes, in a chair with his/her back supported and feet comfortably resting on the floor.

5. Due to the likelihood each arm can have a slightly different BP, it is strongly encouraged to use the same arm that was selected at screening for all measurements, supported at heart level.

6. No restrictive clothing should encircle the arm in which BP measurements are determined.

7. An appropriately sized cuff will be required wherein the cuff bladder encircles at least 80% of the upper portion of the arm.

8. Three serial BP readings will be undertaken with a minimum of 2 minutes between readings and with the cuff fully deflated between each determination.

9. The mean of the second and third of these 3 readings will be used as the study day BP value.

10. All measurements, along with the calculated mean value, will be recorded in the source documents. The mean of the second and third readings will be calculated within the EDC as the study day result.

Appendix 3 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 lupus nephritis

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

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[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.

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Appendix 4 Conversion Table for Oral Corticosteroids

Compound	Equivalent Potency (mg)
Prednisone	5
Prednisolone	5
Cortisone	25
Hydrocortisone (cortisol)	20
Methylprednisolone	4
Triamcinolone	4
Dexamethasone	0.75

i.e.,
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

Appendix 5 1997 Update of the 1982 American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus

Four or More of: Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b) Pericarditis--documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day (or 0.5 mg/mg by UPCR) or greater than 3+ if quantitation not performed OR b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance

Four or More of: Criterion	Definition
9. Hematologic disorder	a) Hemolytic anemia--with reticulocytosis OR b) Leukopenia--less than 4,000/mm^3 total on 2 or more occasions OR c) Lyphopenia--less than 1,500/mm^3 on 2 or more occasions OR d) Thrombocytopenia--less than 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a) Anti-dsDNA: antibody to native dsDNA in abnormal titer OR b) Anti-Sm: presence of antibody to Sm nuclear antigen OR c) Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

Abbreviation: ECG = Electrocardiogram.

Sources: Hochberg MC, MD, MPH for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271-7.

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Appendix 6 Systemic Lupus Erythematosus Disease Activity Measure (SELENA-SLEDAI)

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

Descriptor	Definition	Points
Arthritis	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).	4
Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase or aldolase, or electromyogram changes, or a biopsy showing myositis.	4
Urinary casts	Heme-granular or RBC casts.	4
Hematuria	>5 red blood cells per high powered field. Exclude stone, infection or other causes.	4
Proteinuria	>0.5 g per 24 hours or 0.5 mg/mg UPCR by FMV. New onset or recent increase of more than 0.5 g per 24 hours.	4
Pyuria	>5 white blood cells per high power field. Exclude infection.	4
New rash	New onset or recurrence of inflammatory type rash.	2
Alopecia	New onset or recurrence of abnormal patchy or diffuse loss of hair.	2
Mucosal ulcers	New onset or recurrence of oral or nasal ulcerations.	2
Pleurisy	Pleuritic chest pain with pleural rub or effusion or pleural thickening.	2
Pericarditis	Pericardial pain with at least 1 one of the following: rub, effusion or ECG confirmation.	2
Low complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.	2
Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.	2
Fever	>38°C. Exclude infectious cause.	1
Thrombocytopenia	<100,000 platelets per mm^3.	1
Leukopenia	<3,000 white blood cells per mm^3. Exclude drug causes.	1

Abbreviations: ECG = Electrocardiogram; RBC = Red blood cells; SLE = Systemic lupus erythematosus.

Source: Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang DH, and the Committee on Prognosis Studies in SLE. Derivation of the SLEDAI: a disease activity index for lupus subjects. Arthritis Rheum. 1992;35:S630-40.

Appendix 7 Expanded List of Allowed Concomitant Medications

- Prophylactic therapy for steroid-induced bone loss (calcium with Vitamin D and/or a bisphosphonate).

- Low dose aspirin is allowed for cardiovascular prophylaxis.

- Minor GI AEs (such as nausea, vomiting and diarrhea) may be treated symptomatically (e.g., with loperamide for diarrhea or standard anti-emetics such as metoclopramide or domperidone for nausea and vomiting). Proton pump inhibitors or ranitidine are permitted for dyspepsia or gastric protection. Magnesium or aluminum containing antacids may be used, but should not be taken at the same time as study treatment; such antacids, if required, should be taken either 1 hour before or 2 hours after study treatment.

- Amphotericin or oral nystatin are permitted as infective prophylaxis against fungal infections, and low-dose sulfamethoxazole/trimethoprim is permitted as prophylaxis against *Pneumocystis carinii pneumonia*.

- Granulocyte colony stimulating factor is allowed to manage neutropenia in the presence of major infection (i.e., infections requiring IV antibiotics).

- Oral or IV iron preparations for iron deficiency and/or anemia.

- Erythropoietin is permitted for treatment of severe anemia (hemoglobin <10 mg/dL).

- Cytomegalovirus prophylaxis is permitted for example with oral valganciclovir.

- Acute intermittent administration of NSAIDs for not greater than 7 consecutive days is permitted.

- Lipid-lowering therapies (e.g., statins) will be used as clinically indicated.

- Antimalarials should be prescribed when clinically indicated.

- Angiotensin-converting enzyme inhibitors, ARBs, and aliskerin and other therapies are recommended, as per standard guidelines but if used their dose must be stable throughout the study. In addition subjects must be on a stable dose of ACE inhibitors or ARBs for 4 weeks prior to enrollment.

- In the case of uncontrolled hypertension (systolic BP >165 mmHg or diastolic >105 mmHg on 2 successive measurements), the addition of a diuretic or calcium channel blocker only are permitted, together with dose decreases or

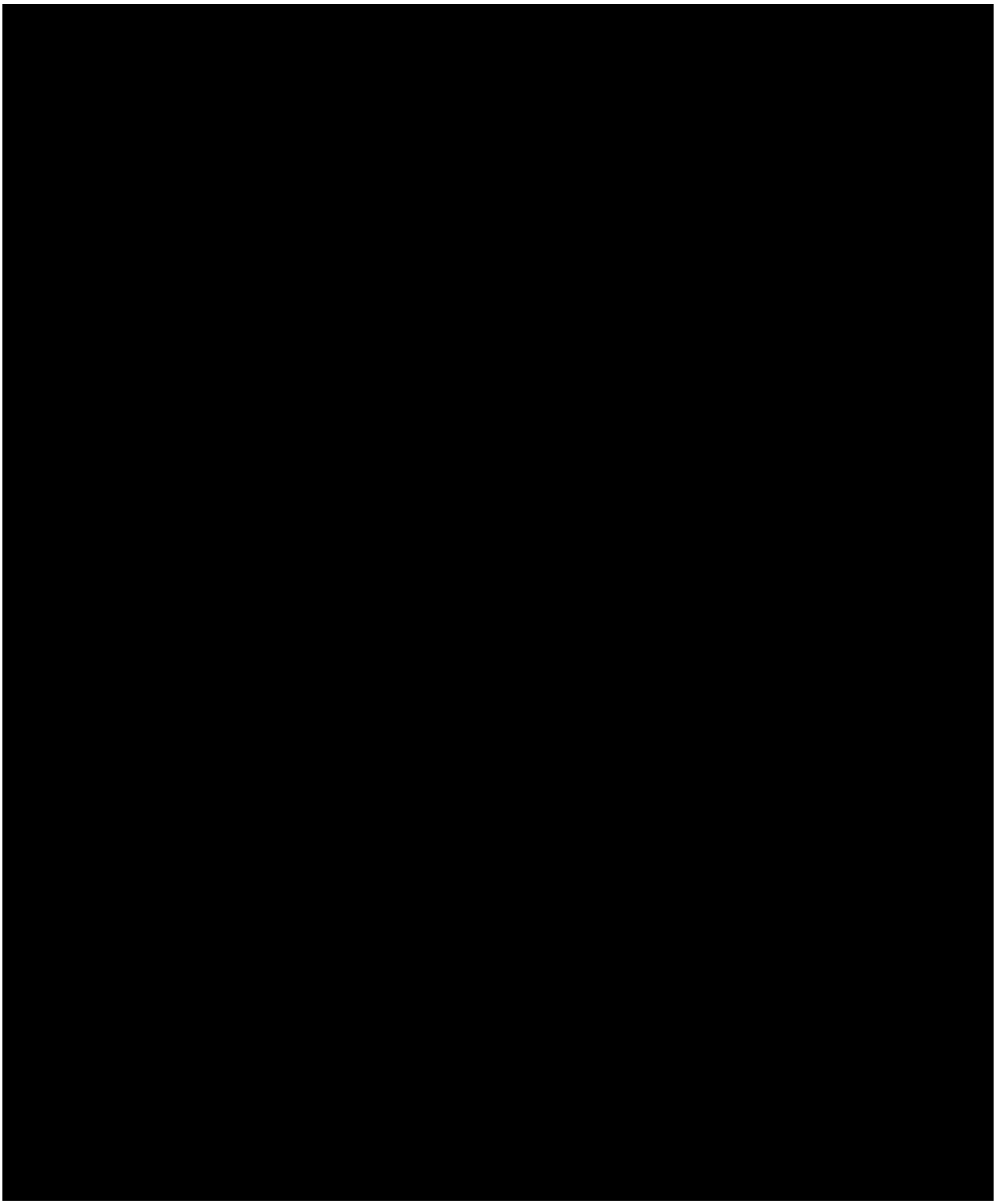
interruption of study treatment per the instructions in Section 7.9, Increased Blood Pressure.

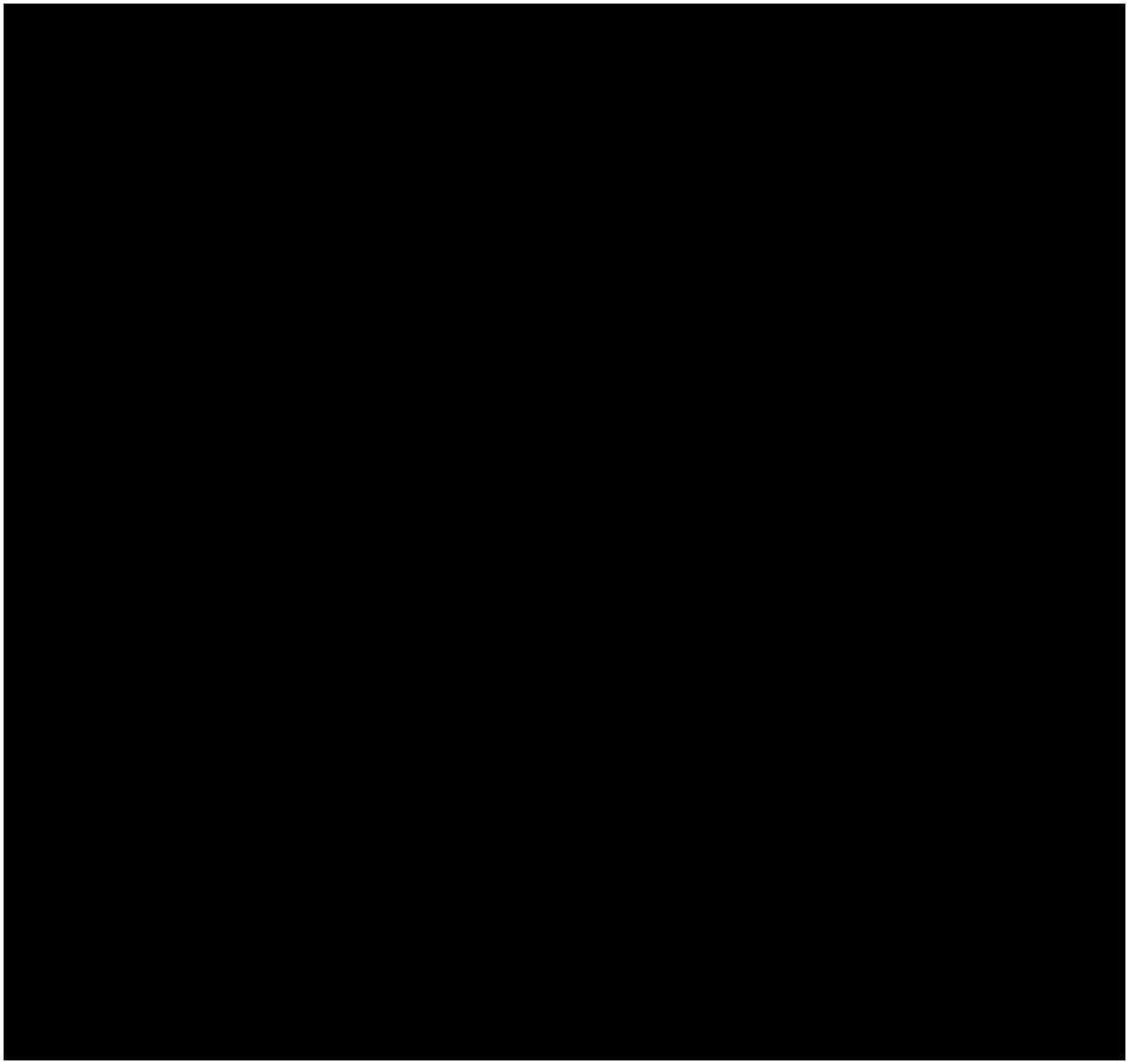
Appendix 8 Summary of Treatment and Food Restrictions

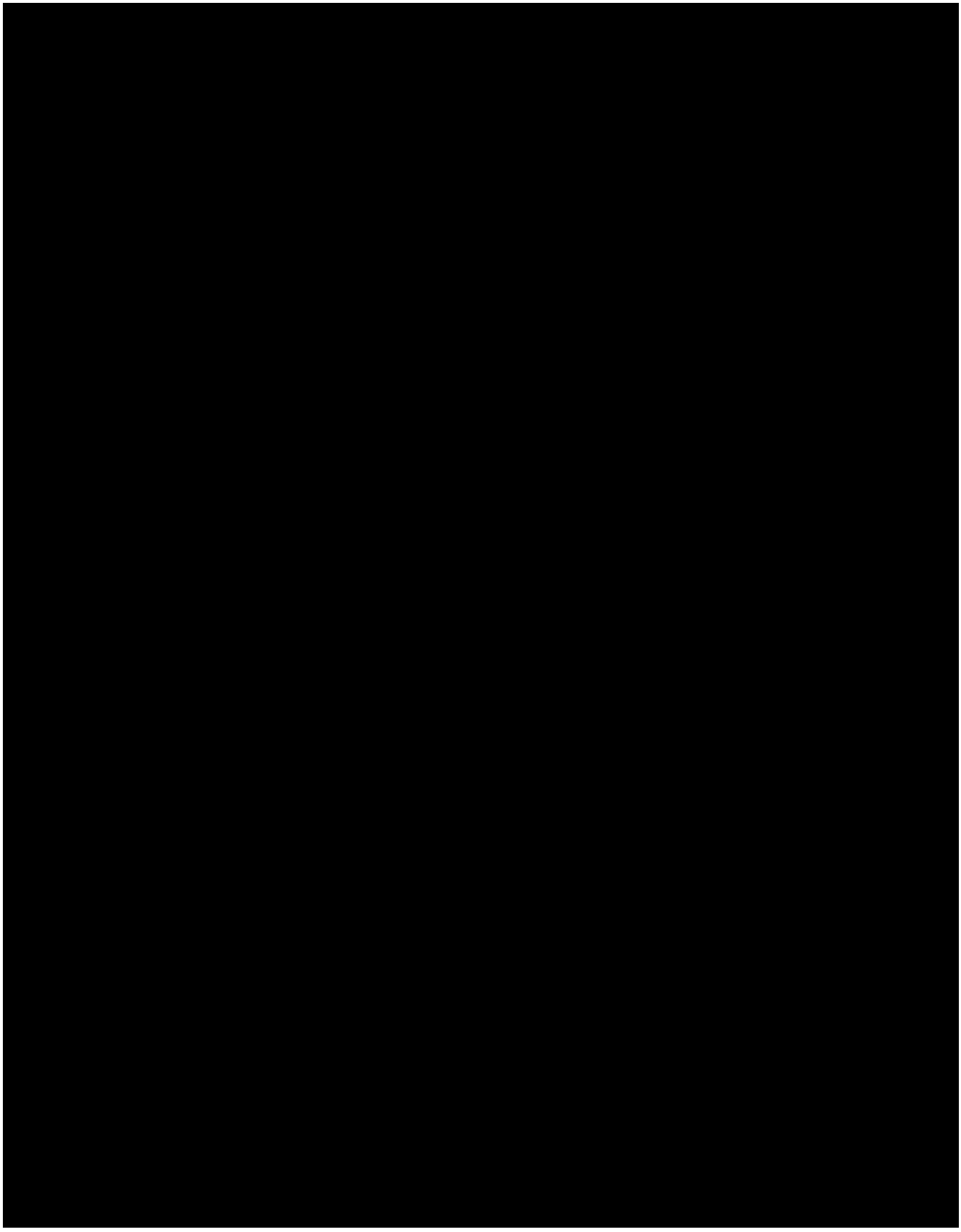
Treatment	Washout Period	During Treatment	Reason
Immunosuppressants other than those allowed by protocol	30 days	Prohibited	Interferes with study efficacy endpoints
Aminoglycosides Amphotericin B Melphalan Ketoconazole Rifampin	14 days	Prohibited	May potentiate toxicity
NSAIDs chronic dosing (>7 consecutive days)	Prohibited	Prohibited	May potentiate nephrotoxicity
P-gp substrates	To be monitored	To be monitored	Drug-drug interaction
P-gp inhibitors	To be discussed with Medical Monitor	To be discussed with Medical Monitor	Drug-drug interaction
Androgenic steroids Cimetidine Fluconazole, itraconazole Macrolide antibiotics (azithromycin, clarithromycin, erythromycin) Metoclopramide Barbiturates and derivatives Carbamazepine Octreotide acetate Phenytoin Sulfadimidine (intravenous) Theophylline	To be discussed with Medical Monitor	To be discussed with Medical Monitor	Drugs interfering with Orelvo metabolism
ACE inhibitors and ARBs	No change or introduction during screening	Change or commencement prohibited	Interfere with primary endpoint assessment
Foods			
Grapefruit and grapefruit juice	24 hours	Prohibited	May affect the metabolism of Orelvo

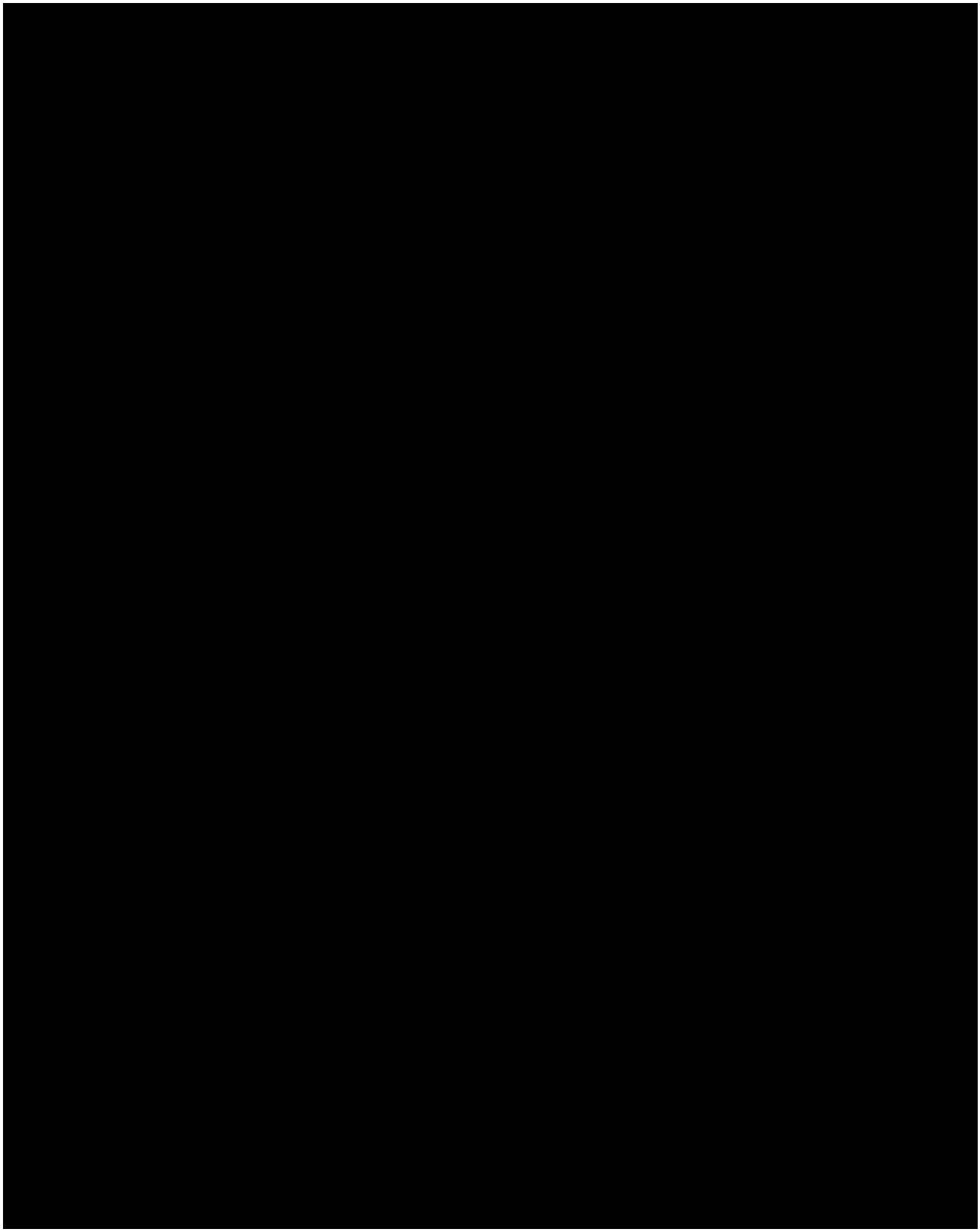
Abbreviations: ACE = Angiotensin converting enzyme; ARB = Angiotensin receptor blocker; NSAID = Non-steroidal anti-inflammatory drug; P-gp = P-glycoprotein.

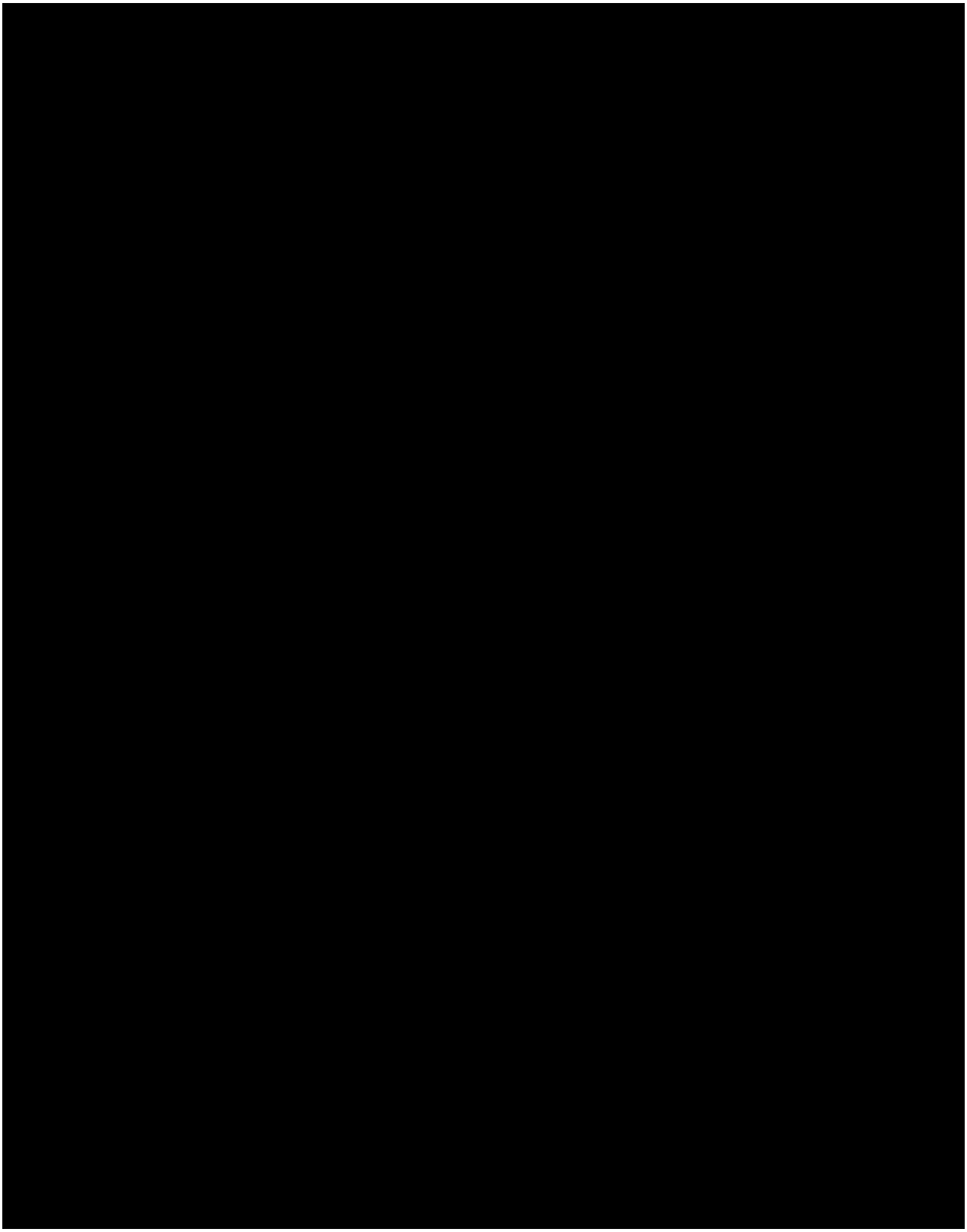
Appendix 9 Short Form Health Survey (SF-36) HRQoL Assessment











Appendix 10 LupusPRO (v1.7) HRQoL Assessment