An Open-Label Dose-Exploration Cohort Study Evaluating the Efficacy and Safety of Voclosporin in Achieving Complete or Partial Remission of Proteinuria in Subjects with Focal Segmental Glomerulosclerosis

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IND Number:	137,905

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DECLARATION OF SPONSOR

Title: An Open-Label Dose-Exploration Cohort Study Evaluating the Efficacy and Safety of Voclosporin in Achieving Complete or Partial Remission of Proteinuria in Subjects with Focal Segmental Glomerulosclerosis

Version Number/Date: Version 4.0 (Amendment 3) / 20 December 2019

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] 10 JAN 2020

Chief Medical Officer — Date (e.g., DD Month Year)

[redacted] 13 JAN 2020

Vice President, Quality and Regulatory Affairs — Date (e.g., DD Month Year)

INVESTIGATOR AGREEMENT FORM

I have read the attached protocol titled: *An Open-Label Dose-Exploration Cohort Study Evaluating the Efficacy and Safety of Voclosporin in Achieving Complete or Partial Remission of Proteinuria in Subjects with Focal Segmental Glomerulosclerosis*

Version Number/Date: Version 4.0 (Amendment 3) / 20 December 2019

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.

<insert name> Principal Investigator	Date (e.g., DD Month Year)

SYNOPSIS

Title:	An Open-Label, Dose-exploration, Cohort Study Evaluating the Efficacy and Safety of Voclosporin in Achieving Complete or Partial Remission of Proteinuria in Subjects with Focal Segmental Glomerulosclerosis
Short Title:	AURONA
Study Product:	Voclosporin
Indication:	Focal Segmental Glomerulosclerosis
Phase:	2
Sponsor:	Aurinia Pharmaceuticals Inc.
Study Code:	AUR-VCS-2017-03
Objectives:	Primary Objective: • To assess the efficacy of voclosporin in achieving complete or partial remission of proteinuria after 24 weeks of therapy in subjects with focal segmental glomerulosclerosis (FSGS). Secondary Objective: • To assess the safety and tolerability of voclosporin over 24 weeks in subjects with FSGS.
Design:	Open-label, 24-week, multicenter, exploratory cohort study of voclosporin.
Treatment:	Investigational Treatment: Voclosporin softgel capsules containing 7.9 mg drug. Up to 10 subjects will be enrolled into Cohort 1 and take voclosporin 23.7 mg orally (PO), twice daily (BID). The dose level of voclosporin for Cohort 2 (at least 10 subjects) will be determined by analysis of efficacy and safety data at Week 12 from the first 5-6 subjects in Cohort 1.
Inclusion Criteria:	1. Written informed consent before any study-specific procedures are performed. 2. Male or female subjects with a minimum age of 18 years (or legal age of consent if >18 years) to 75 years of age, inclusive, at the time of consent. 3. Primary FSGS diagnosed by renal biopsy within 6 months prior to the screening visit. Biopsy results over 6 months prior to screening may be permitted following review with the Medical Monitor to confirm eligibility.

Inclusion Criteria (cont'd):	4. At initial screening assessment and at last qualifying assessment during screening period prior to baseline, FSGS subjects must have a urine protein creatinine ratio (UPCR) of ≥2.0 mg/mg. Subjects can be treatment-naïve or receiving steroid treatment (oral or IV) for FSGS. Subjects taking steroids must show signs of improvement in proteinuria, defined as at least a 20% improvement in UPCR from initiation of steroids to the last stability assessment prior to baseline. Subjects who have discontinued steroid treatment due to poor tolerability may be considered for the study. Subjects should also have a serum albumin level of ≤3.2 g/dL at screening and at the last qualifying assessment prior to baseline; subjects with serum albumin >3.2 g/dL may be included following review to confirm primary FSGS and after discussion with the Medical Monitor. 5. All subjects should be treated with angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) unless they have documented intolerance or contraindication to these medications. Doses of these agents must be stable for at least 2 weeks prior to baseline, with blood pressure (BP) ≤150/90 mmHg at the baseline visit (Visit 2). a) Subjects with nephrotic edema may be treated with diuretics during the screening period. Volume status should be optimized based on the clinical judgment of the Investigator and the doses of diuretics must be stable for at least 2 weeks prior to baseline. b) At the discretion of the Investigator, subjects with hyperlipidemia may be treated with lipid-lowering agents (e.g., statins) in accordance with standard clinical practice. Doses must be stable for at least 2 weeks prior to baseline. 6. Stable proteinuria, renal function, and BP for at least 2 weeks prior to baseline, as assessed by the Investigator. Changes in UPCR, estimated glomerular filtration rate (eGFR), and/or BP during the screening period may be due to treatments administered (e.g., ACEIs and ARBs); and, therefore, may interfere with study assessments or outcomes, or may place the subject at increased risk. All subjects must be discussed with the Medical Monitor prior to initiation of study treatment. 7. Women of childbearing potential must have a negative serum pregnancy test prior to dispensing study treatment. Two effective forms of contraception must be used simultaneously unless abstinence is the chosen method. Subjects must use effective contraception during the study.
Exclusion Criteria:	1. Subjects unable or unwilling to give written informed consent and/or to comply with study procedures. 2. Clinical or histologic evidence of secondary FSGS. 3. Histologic evidence of collapsing variant FSGS. 4. eGFR as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation of ≤30 mL/minute/1.73 m^2 at initial screening assessment or ≤45 mL/minute/1.73 m^2 at last qualifying assessment during screening period prior to baseline.

Exclusion Criteria (cont'd):	5. Currently taking or expected to require any of the prohibited medications listed in the protocol at screening or during the study. This includes prior use of cytotoxic or other immunosuppressant treatment for FSGS. Subjects who have discontinued steroid treatment due to lack of response are excluded from the study. 6. Currently requiring renal dialysis (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study period. 7. A previous renal transplant or planned renal transplant during the study. 8. Body mass index >40 kg/m^2 at last stability assessment. 9. Family history of nephrotic syndrome. 10. Any known hypersensitivity or contraindication to cyclosporine, or components of any cyclosporine drug product. 11. 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. • Current or past 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. 12. Other clinically significant active medical conditions, such as: • Severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome. Subjects with 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 are excluded. • Liver dysfunction: aspartate aminotransferase, alanine aminotransferase, or bilirubin ≥2.5 times the upper limit of normal at last qualifying assessment during screening period prior to baseline. • Chronic obstructive pulmonary disease or asthma requiring oral steroids.

Exclusion Criteria (cont'd):	• Bone marrow insufficiency: white blood cell count <2,500/mm^3, absolute neutrophil count <1.3 × 10^3/μL, and/or thrombocytopenia (platelet count <50,000/mm^3) at screening or at last qualifying assessment during screening period prior to baseline. • Current infection requiring intravenous antibiotics. 13. Any overlapping autoimmune condition for which the condition or the treatment of the condition may affect the study assessments or outcomes (e.g., any condition for which additional immunosuppression, including systemic corticosteroids, and/or cytotoxic therapy is indicated). Overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes are not excluded. 14. No vaccines using live organisms, viral or bacterial, are allowed during screening and while taking the study treatment. 15. 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. 16. 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. 17. Subjects who are pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions. 18. 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. 19. Subjects treated in a previous voclosporin clinical study.
Primary Endpoint:	Proportion of subjects with remission of proteinuria at Week 24, assessed overall and for each individual cohort, based on the following parameters: • Complete remission: UPCR of <0.3 mg/mg OR • Partial remission: UPCR ≥0.3 mg/mg and <3.0 mg/mg with >50% reduction in UPCR from baseline
Secondary Endpoints:	The following secondary endpoints will be assessed overall and for each individual cohort: • Proportion of subjects with complete remission or partial remission of proteinuria at Weeks 8 and 12 • Proportion of subjects with complete remission of proteinuria at Weeks 8, 12, and 24 • Proportion of subjects with UPCR <0.5 mg/mg at Weeks 8, 12, and 24 • Proportion of subjects with partial remission of proteinuria at Weeks 8, 12, and 24

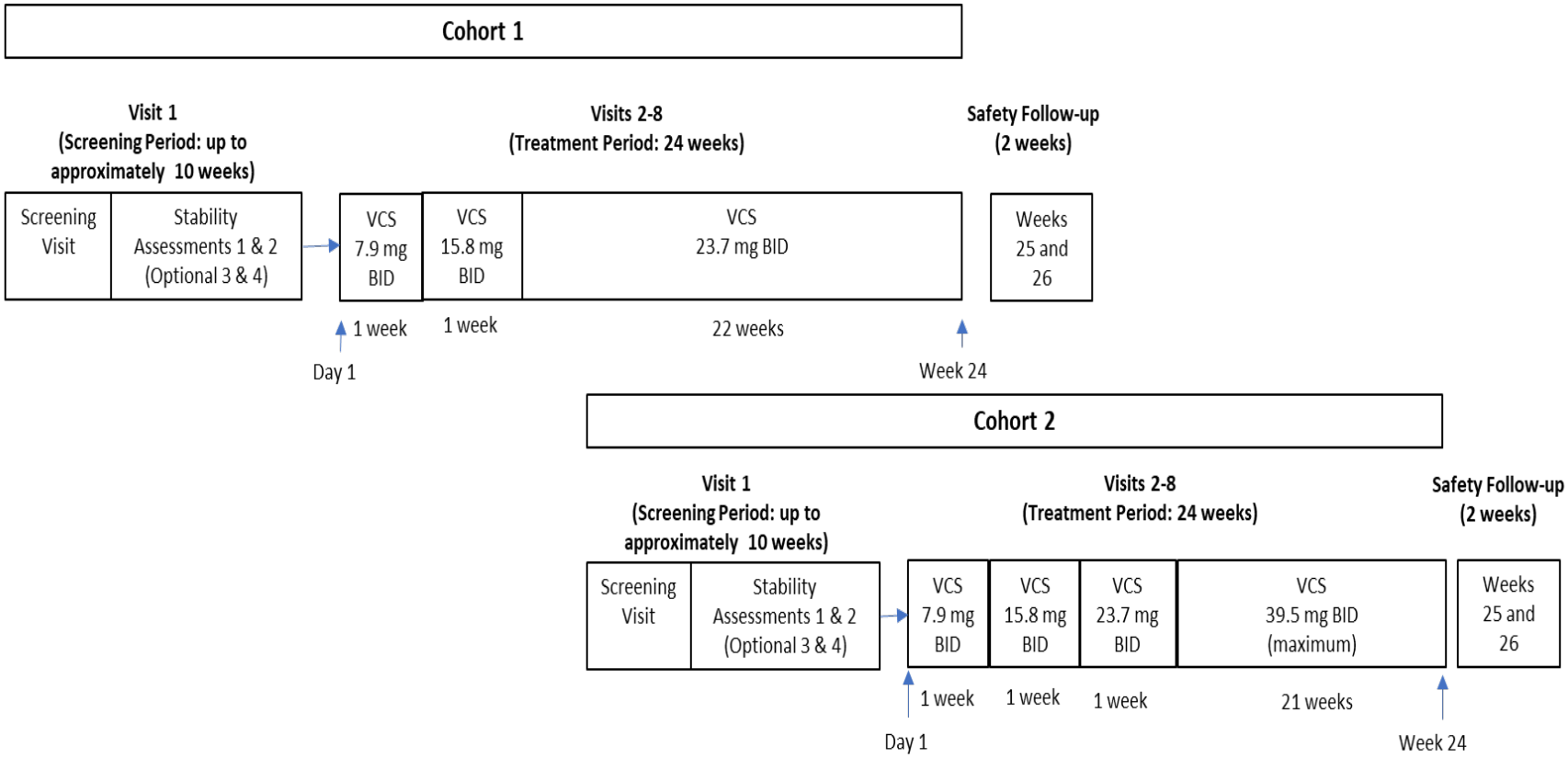
Secondary Endpoints (cont'd):	• Time to first occurrence of complete or partial remission of proteinuria • Time to first occurrence of complete remission of proteinuria • Time to first occurrence of partial remission of proteinuria • Time to first occurrence of 50% reduction in UPCR from baseline • Duration of UPCR <0.3 mg/mg • Change from baseline in UPCR at each time point • Proportion of subjects with a confirmed >30% decrease from baseline in eGFR (utilizing the CKD-EPI formula) at each time point • Proportion of subjects with a confirmed >30% increase in eGFR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10) • Change in UPCR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10) • Change in eGFR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10) • Change from baseline in serum creatinine, serum albumin, and eGFR at each time point • Quality of life assessments – Mean change in Patient Reported Outcome Measurement Information System (PROMIS) measures at Week 24 – Change from baseline in Kidney Disease Quality of Life-Short Form (KDQOL-SF™) score at Week 24 • Safety and tolerability over 24 weeks • Renal biopsy: descriptive analyses of changes in histopathology will be evaluated in post-treatment (24 weeks) renal biopsies in a subset of patients • Change from baseline to Weeks 4 and 24 in the following biomarkers: – Urine nephrin – Urine synaptopodin – Serum transforming growth factor beta

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. Subjects will be assigned a unique subject number which will be used to identify them throughout the study. If a subject has not had a renal 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 the end of screening. The duration of the screening period will be approximately 4 weeks to 10 weeks (allowing for visit windows) to ensure that subjects meet eligibility criteria, including renal disease stability assessments. The first 5-10 subjects meeting the required eligibility criteria will be assigned to Cohort 1 and will receive voclosporin according to the following dosing regimen: • Week 1: 1 capsule (7.9 mg) PO, BID • Week 2: 2 capsules (15.8 mg) PO, BID • Week 3 – Week 24: 3 capsules (23.7 mg) PO, BID Appropriate sponsor personnel (including the medical monitor) and the investigator will jointly decide whether to continue with the dose escalation for each subject. When the first 5 or 6 subjects in Cohort 1 have completed 12 weeks of treatment with voclosporin, the top line efficacy and safety data will be analyzed to determine the dose level for Cohort 2. The selected dose may be higher or lower than 23.7 mg BID. The maximum dose possible for Cohort 2 will be 39.5 mg (5 capsules) BID. Should this dose be selected the following dosing regimen will be followed: • Week 1: 1 capsule (7.9 mg) PO, BID • Week 2: 2 capsules (15.8 mg) PO, BID • Week 3: 3 capsules (23.7 mg) PO, BID • Week 4 – Week 24: 5 capsules (39.5 mg) PO, BID Evaluable safety and tolerability data at Week 12 from the first 5-6 subjects from Cohort 1 are required in order to make the decision to escalate to a higher dose level for Cohort 2. As a guidance, the dose will not be escalated if any of following criteria are met in the first 5 or 6 subjects from Cohort 1, unless it was obvious that the occurrence was not related to the administration of voclosporin: • Severe adverse events (SAEs) of same character in ≥2 subjects. • Clinically significant decrease in eGFR in ≥5 subjects. • Clinically significant laboratory abnormalities of same character in ≥5 subjects. • Clinically significant abnormalities of electrolytes in ≥4 subjects. • Clinically significant changes in vital signs of same character in ≥4 subjects.

Procedures (cont'd)	Doses and dose increments smaller than anticipated may be proposed for Cohort 2 based on the safety and tolerability results from the Cohort 1. All subjects will complete dosing through 24 weeks of study treatment and will have 2 Safety Follow-Up visits, 1 and 2 weeks after completion of treatment (i.e., at Week 25 and Week 26). Subjects who permanently discontinue study treatment before the Week 24 visit will return for all remaining study visits and assessments, including the 2 Safety Follow-Up visits, unless they have withdrawn consent.
Sample Size:	As this is an exploratory study, sample size calculations are not required. It is estimated that approximately 20 subjects will be recruited, with up to 10 subjects in Cohort 1 and at least 10 subjects in Cohort 2.
Statistical Methods:	<u>Analysis:</u> All statistical analyses relating to the primary and secondary objectives will be undertaken at study closure and will incorporate all available data. Given the small sample size, all analyses will be descriptive in nature. Confidence intervals (CIs) for proportions may be calculated but it is recognized that such intervals, being based on 20 patients, will be very wide. As an example, the 95% Clopper-Pearson CI for a proportion of 30% based on 20 patients is (11.9%, 54.3%). <u>Populations:</u> The efficacy analysis will be based on intent-to-treat (ITT) principles and will include all enrolled subjects (non-screening failures). The per-protocol data set will include the subset of subjects in the ITT set who do not have any major protocol violations (to be defined). The safety analysis set will consist of all subjects who receive at least 1 dose of study treatment. <u>Methods:</u> Top line efficacy (change from Baseline in UPCR) and safety data (AEs, eGFR, ECGs and vital signs) for the first 5 or 6 subjects in Cohort 1 completing 12 weeks of study treatment will be reviewed and based on those data the commencement of enrollment and the target dose for Cohort 2 will be determined. The analysis of the primary endpoint, complete or partial remission of proteinuria at Week 24, will be conducted on the ITT set and confirmed with the per-protocol set (if applicable). Remission of proteinuria will be summarized and an exact 2-sided 95% CI for the remission rate will be calculated. The analyses of the secondary endpoints will incorporate the use of 2-sided 95% CIs and are described below: • Binary endpoints will be summarized using exact 2-sided 95% CIs. • Endpoints measured as a time-to-event will be displayed using Kaplan-Meier methodology. Median time-to-event along with 2-sided 95% CIs will be displayed.

Statistical Methods (cont'd)	• Other endpoints will be summarized by visit. Absolute values and differences between baseline and each time point up to and including Week 24 will be summarized using means and 2-sided 95% CIs. Changes between last on treatment value and post treatment follow-up will also be summarized. <u>Safety Endpoints:</u> Adverse events will be aggregated by System Organ Class and preferred term and presented as summary tables. Laboratory values, 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. Exploratory analyses will be undertaken should the data suggest areas worthy of further investigation.

STUDY SCHEMA



Notes: BID=Twice daily; VCS=Voclosporin.

AUR-VCS-2017-03 SCHEDULE OF EVENTS

Visit	**Visit 1 Screening Period**		**Visit 2 Baseline**	**Visit 3**	**Visits 4-5**	**Visit 6**	**Visit 7**	**Visit 8 End of Treatment/ Early Termination**	**Visit 9 Safety Follow-up**	**Visit 10 Safety Follow-up**
Day/Week	**Screening to Day -1**		**Day 1 (Within 1 Wk Post Qualifying Assessment)**	**Wk 2 (±3 Days)**	**Wks 4, 8 (±3 Days)**	**Wk 12 (±3 Days)**	**Wk 18 (±5 Days)**	**Wk 24 (±7 Days)**	**Wk 25 (±3 Days) or Premature Disc. +7 Days**	**Wk 26 (±3 Days) or Premature Disc. +14 Days**
	Screening Visit[1]	**Stability Assessments 1 & 2, Optional 3 & 4[1]**								
Informed consent	✓									
Eligibility criteria	✓	✓								
Renal biopsy[2]								✓[2]		
Medical history and demography	✓									
Physical exam[3]	✓		✓					✓		
Vital signs[4]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECG[5]	✓		✓					✓		
Laboratory assessments[6]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pharmacokinetics[7]					✓			✓		
Urinalysis and urine microscopy	✓		✓	✓	✓	✓	✓	✓	✓	✓
FMV urine collection[8]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
24-hour urine[9]			✓			✓		✓		
QoL[10]			✓					✓	✓	✓
Pregnancy test[11]	✓	✓	✓	✓	✓	✓	✓	✓		
Adverse events	✓[12]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense study medication/ compliance[13]			✓	✓	✓	✓	✓	✓[14]		
First dose of study medication			✓[15]							

1 Stability assessments to occur at 14-day intervals (± 3 days) with first assessment approximately 2 weeks after the screening visit. Stability assessments 1 and 2 are mandatory; assessments 3 and 4 are optional if additional time is required for the subject's clinical status to stabilize. Note that the laboratory assessments and FMV results of the last stability assessment will be used as the qualifying values for eligibility. Enrollment of eligible subjects must occur within 1 week of the final stability assessment.

2 If a subject has not had a recent renal biopsy, one may be performed to assess eligibility for the study provided informed consent has been given. The biopsy must have been performed 6 months prior to the screening visit. Biopsy results over 6 months prior to screening may be permitted following review with the Medical Monitor to confirm eligibility. Repeat renal biopsies may be done at Week 24 in a subset of subjects at selected sites.

3 Complete physical exam at screening; abbreviated exam at all other visits.

4 BP, pulse, temperature, weight, and height. Height included at initial screening assessment only. At stability assessments, BP only will be included.

5 In the event that a subject is noted to have a QTcF value exceeding 500 msec, or an increase of >60 msec from baseline, the ECG should be repeated within 24 hours. Further details provided in the study protocol.

6 Laboratory assessments will be performed according to the schedule in the study protocol. Subjects must be fasting for at least 8-12 hours at Baseline and at end of study/early termination visit.

7 Pharmacokinetic assessments will be done at Weeks 4 and 24. PK samples will be drawn prior to study treatment dosing (trough sample), and at 1, 2 and 4 hours post-dose. In the event a subject experiences an SAE or requires a dose modification or is withdrawn from treatment, a voclosporin sample should be taken, with a trough sample preferred.

8 The UPCR will be calculated both from the FMV and from standard urinalysis results. If the FMV 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.

9 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.

10 Patient Reported Outcome Measurement Information system (PROMIS) and Kidney Disease Quality of Life-Short Form (KDQOL-SF™).

11 Serum pregnancy test to be evaluated at central laboratory at Screening and Week 24; urine pregnancy test will be performed locally at all other visits as applicable.

12 If screening visit occurs on the same day as informed consent, any findings are to be recorded as Medical History. Any change since the date of signed consent and/or during the screening period would be considered an AE.

13 Subjects in Cohort 1, will be contacted by telephone at the end of Week 1 as a reminder to increase their dose to 2 capsules (15.8 mg) BID for 1 week, starting at Week 2. Subjects will be contacted again by telephone at the end of Week 2 as a reminder to increase their dose to 3 capsules (23.7 mg) BID, starting at Week 3, for the remainder of the treatment period. Subjects in Cohort 2, will also be contacted at the end of each week (as required) up to Week 4, as a reminder to increase their dose to the maximum selected for Cohort 2.

14 Compliance only.

15 First dose of study medication should occur in the morning the day after dispensing.

Notes: Subjects who discontinue therapy will be requested to attend their regularly scheduled study visits to the end of the study.
AE = Adverse event; BID = Twice daily; BP = Blood pressure; Disc. = Discontinuation; ECG = Electrocardiogram; FMV = First morning void; Min = Minimum; QoL = Quality of life; QTcF = QT interval duration corrected for heart rate using method of Fridericia; SAE = Serious adverse event; Wk= Week.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF APPENDICES

Page

LIST OF ABBREVIATIONS

ACEI	Angiotensin converting enzyme inhibitor
ADR	Adverse drug reaction
AE	Adverse event
ARB	Angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical
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
Aurinia	Aurinia Pharmaceuticals Inc.
BID	Twice daily
BP	Blood pressure
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
DEX	Dexamethasone
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FMV	First morning void
FSGS	Focal Segmental Glomerulosclerosis
GCP	Good Clinical Practice
GI	Gastrointestinal

GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISA247	Voclosporin
ITT	Intent-to-treat
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDQOL-SF™	Kidney Disease Quality of Life-Short Form
LN	Lupus nephritis
MMF	Mycophenolate mofetil
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PD	Pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetic
PO	Orally
PPS	Per-protocol set
PROMIS	Patient Reported Outcome Measurement Information System
QoL	Quality of life
QTcF	QT interval duration corrected for heart rate using method of Fridericia
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
$t_{1/2}$	Terminal elimination half-life

TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor beta
UPCR	Urine protein creatinine ratio

1. INTRODUCTION AND BACKGROUND

1.1 Background of the Disease and Treatment Options

Focal segmental glomerulosclerosis (FSGS) is diagnosed by characteristic glomerular findings of podocyte injury evidenced by findings from immunofluorescence and electron microscopy following renal biopsy. The disease is categorized as primary (i.e., idiopathic FSGS) or secondary (e.g., adaptive changes resulting from glomerular hyperfiltration in conditions such as reflux nephropathy, obesity, and reduced nephron mass; drug-induced FSGS; and FSGS associated with viral diseases) [1].

The predominate clinical feature of primary FSGS is proteinuria, typically with signs and laboratory abnormalities associated with nephrotic syndrome (i.e., total urine protein >3.5 g/day, edema, hypoalbuminemia, and hypercholesterolemia) [1]. Patients may experience renal dysfunction which can progress to end-stage renal disease (ESRD). Reportedly 50%-60% of patients have nephrotic syndrome at presentation, and approximately 50% of adult patients with idiopathic nephrotic syndrome are diagnosed with FSGS [1]. The amount of proteinuria at presentation and lack of response to treatment are correlated with progression to ESRD. FSGS is more common in males than in females and, in racially diverse populations, more common in black patients than in white patients [1].

Several published reviews have summarized the histopathologic features of FSGS and mechanisms of podocyte injury, disruption of the glomerular filtration barrier, and progression of renal dysfunction, e.g., D'Agati [1] and Kikuchi et al [2].

The glomerular filtration barrier consists of glomerular endothelial cells, the glomerular basement membrane, and epithelial cells (podocytes). There is a complex interaction between these elements; the podocyte is not only a critical part of the structure, providing structural support to glomerular capillary, but also plays a role in maintaining the glomerular basement membrane and slit diaphragm proteins that permit filtration of water and small molecules and retention of large molecules and cells. Light microscopy findings include a segmental pattern of mesangial sclerosis occurring in some (i.e., focal), but not all glomeruli, without typical features of other proteinuric glomerulopathies. Immunofluorescence microscopy does not reveal immune deposits. The primary pathophysiologic mechanism of FSGS is reflected in electron microscopy findings, which include typical abnormalities of podocyte morphology, i.e., diffuse podocyte foot process effacement. In FSGS, as in other podocytopathies, these abnormalities disrupt the glomerular filtration barrier, resulting in protein leakage.

The etiology of primary (idiopathic) FSGS is not known and is likely multifactorial. Based on indirect evidence, development of FSGS has been attributed to circulating factors (e.g., cytokines such as cardiotrophin-like cytokine 1, anti-CD40 (podocyte-B7-1 antigen) antibody, apolipoprotein A-Ib (ApoA-Ib) and serum soluble urokinase-type plasminogen activator receptor (suPAR)) which may mediate glomerular permeability. FSGS recurs in transplanted

kidneys, and proteinuria can be reduced by plasmapheresis in these patients; plasma and sera from FSGS patients have induced proteinuria in rats and in isolated rat glomeruli [3]. Several immune mechanisms have also been postulated to contribute to progressive glomerular damage subsequent to the initial podocyte injury, including cellular immunity and autoimmune reactivity [4].

Elevated levels of transforming growth factor-beta (TGF-β) have been implicated in the pathogenesis of FSGS and have been reported in numerous tissues of patients with FSGS including the tubule-interstitium and the glomerular epithelial cells [5,6]. Calcineurin α, one of the calcineurin isoforms, is involved in broad cellular tasks including protein folding and regulation of TGF-β expression. The use of an immunosuppressive agent that increases TGF-β levels may have a negative long-term impact on renal fibrosis, whereas the use of an immunosuppressive agent that either decreases or has no impact on TGF-β levels may stabilize presently existing renal fibrosis. Concerning the podocyte, Liao et al [7] showed that in a murine (MRL/lpr) model, the calcineurin inhibitor (CNI) tacrolimus may decrease TGF-β-induced podocyte apoptosis, suggesting that calcineurin may play a role in the progression of renal disease, thereby suggesting a potential mechanism of CNI benefit.

1.1.1 Limitations of Current Treatment

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis [8] provides Level 2C (low) and 2D (very low) suggestions for the treatment of primary FSGS: Corticosteroids are suggested as initial treatment at a daily single dose of 1 mg/kg (maximum 80 mg) or 2 mg/kg (maximum 120 mg) (Level 2C), to be administered for a minimum of 4 weeks and maximum of 16 weeks, as tolerated, or until complete remission has been achieved, whichever is earlier (Level 2D). Calcineurin inhibitors are suggested for use in FSGS as second-line treatment after failure of remission with steroid treatment and as first-line treatment in patients with relative contraindications to steroids. (Level 2D) (see Section 1.2.1, Mechanism of Action of CNIs and Potential for Treatment Benefit in FSGS). Up to 50% of patients fail to respond to corticosteroids [1]. Earlier use of CNIs in primary FSGS, as initial treatment at the time of diagnosis, would avoid the risks of corticosteroid use, and may result in proteinuria remission, as well as potentially decrease the risk of progression to ESRD.

The potential benefit of voclosporin in treatment-naïve FSGS patients is supported by the mechanism of action of CNIs (see Section 1.2.1, Mechanism of Action of CNIs and Potential for Treatment Benefit in FSGS) and clinical data suggesting benefit in steroid-resistant patients (see Section 1.2.2, Clinical Studies of CNIs in FSGS), as well as potential advantages of voclosporin over cyclosporine (i.e., increased potency demonstrated in nonclinical studies with voclosporin, more predictable pharmacokinetic (PK)/pharmacodynamic (PD) profile (obviating the need for therapeutic drug monitoring), and a potentially improved safety profile compared to cyclosporine A (CsA)) (see FSGS Investigator's Brochure (IB) [9]). These data, with the demonstrated efficacy in renal response (including reduction in proteinuria), suggest

that voclosporin may benefit patients with FSGS. Although treatment guidelines suggest corticosteroids as first line therapy in these patients [8], there are no data to support the use of corticosteroids instead of CNIs in this setting. Corticosteroids are associated with significant toxicities, and if voclosporin demonstrates treatment benefit and an acceptable safety profile, it would provide an appropriate alternative treatment to corticosteroids in this setting.

1.2 Rationale for the Use of Calcineurin Inhibitors in FSGS

Calcineurin inhibitors are suggested for use in FSGS as second line treatment after failure of remission with steroid treatment and as first line treatment in patients with relative contraindications to steroids. In addition to well-characterized immunomodulatory effects, CNIs have been demonstrated to have direct beneficial effects on podocytes that are likely mechanisms of amelioration of proteinuria in podocytopathies, including FSGS.

1.2.1 Mechanism of Action of CNIs and Potential for Treatment Benefit in FSGS

Calcineurin inhibitors have beneficial effects in diseases characterized by disorders of the immune system and in the prevention of rejection after solid organ transplantation by inhibiting activation of nuclear factor of activated T-cell (NFAT) with subsequent regulation of the production of T-cell cytokines [9]. Recently, several investigations have demonstrated that CNIs have non-immunologic effects that contribute to their anti-proteinuric effects in podocytopathies. 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 protected from degradation. Calcineurin dephosphorylates synaptopodin allowing its degradation, with subsequent alteration of the actin cytoskeleton, disruption of the glomerular filtration barrier, and proteinuria. Expression of activated calcineurin in podocytes leads to proteinuria. Thus, by inhibiting calcineurin, CNIs exert a specific anti-proteinuric effect by preventing the degradation of the podocyte stabilizing protein synaptopodin [10,11]. In addition to effects on synaptopodin, cyclosporine has been found to stabilize other components of the actin cytoskeleton, i.e., cofilin-1 and nephrin. Podocyte apoptosis can be induced in the rat purine aminonucleoside model [12]. Shen et al [13] demonstrated that cyclosporine and tacrolimus reduced podocyte apoptosis in the rat purine aminonucleoside model. In addition, inhibition of NFAT signaling in the podocyte by CNIs may ameliorate podocyte injury [14]. Wakamatsu et al [15] evaluated the effects of tacrolimus in a nephrotic rat model (anti-nephrin antibody-induced nephropathy). Utilizing immunohistological analyses of rat and human kidneys, these investigators demonstrated that calcineurin is an element of the slit diaphragm and associated with nephrin, a critical component of the slit diaphragm. In the nephrotic rat model, they demonstrated that calcineurin distribution was altered and calcineurin activity was increased; these abnormalities were prevented by administration of tacrolimus, with amelioration of proteinuria. As noted in Section 1.1,

Background of the Disease and Treatment Options, calcineurin may also contribute to TGF-β-induced fibrosis.

In summary, CNIs, in addition to their immunomodulatory effects have been demonstrated to have direct beneficial effects on podocytes via multiple mechanisms. These effects are likely mechanisms of amelioration of proteinuria in podocytopathies, including FSGS.

1.2.2 Clinical Studies of CNIs in FSGS

The KDIGO guidelines suggest CNIs for use in the first line treatment of FSGS in patients who are intolerant or have contraindications to corticosteroid use [8]. There are no prospective, randomized trials of CNIs (either cyclosporine or tacrolimus) used as first line treatment in adult patients (or children) with FSGS. Limited retrospective observational data support their use in this setting; a recent treatment review [16] cites two studies: Duncan et al [17] and Goumenos et al [18].

In a single study center by Duncan et al [17], 6 patients with biopsy-proven FSGS and nephrotic syndrome, who had been previously treated with angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), but not immunosuppression (including corticosteroids), were treated with tacrolimus and followed prospectively. The mean duration of nephrotic syndrome prior to treatment with tacrolimus was 13.6 months (standard deviation (SD) 11.8); baseline urine protein was 11.0 g/day (SD 4.5) and baseline estimated glomerular filtration rate (eGFR) was 71.7 mL/min/1.73 m^2 (SD 22.4). After approximately 12 months of follow-up, all 6 patients achieved remission, defined as normalization of serum albumin and resolution of edema. Mean urine protein decreased from 11.0 g/day (SD 4.5) to 2.8 g/day (SD 2.5). Reportedly, no patients relapsed after attaining remission.

In a retrospective review by Goumenos et al [18], 51 patients with biopsy-proven FSGS, proteinuria >1 g/day, and serum creatinine <2.5 mg/dL, were followed for 5 years. Of the 51 patients, 26 were treated with conservative management (including ACEIs and other anti-hypertensives) and 25 were treated with immunosuppressive drugs, including prednisolone alone (9 patients, treated for 16 months, 8 with nephrotic syndrome), prednisolone and azathioprine (6 patients, treated for 18 months, 5 with nephrotic syndrome) and prednisolone (0.5 mg/kg/day) and cyclosporine (10 patients, treated for 25 months, 7 with nephrotic syndrome). No patients received cyclosporine monotherapy. Treatment assignment was reportedly based on renal impairment and degree of proteinuria. Remission of nephrotic syndrome (both complete remission (defined as urine protein <0.3 g/day) and partial remission (defined as urine protein between 0.3 and 3 g/day)) occurred in 5/8 patients treated with prednisolone alone, 4/5 patients treated with prednisolone and azathioprine, and 6/7 patients treated with prednisolone and cyclosporine.

Evidence to support the use of CNIs in adult patients who are steroid resistant includes randomized clinical trials as well as observational data. A Cochrane Review published in

2008 [19] identified one blinded controlled study (Cattran et al, 1999 [20]) which evaluated the effect of cyclosporine on remission of proteinuria and ESRD in steroid-resistant adult patients with nephrotic syndrome. This study was a single blind, randomized, placebo-controlled trial in which 26 patients were treated with cyclosporine and low dose prednisone and 23 patients were treated with placebo and low-dose prednisone. Complete remission (urine protein ≤0.3 g/day with stable renal function) or partial remission (50% reduction and ≤3.5 g/day with stable renal function) occurred in 69% of the cyclosporine group and 4% of the placebo group at 26 weeks ($p<0.001$). At 4 years, the renal survival rate was 72% in the cyclosporine group and 49% in the placebo group.

Laurin et al [21] performed a meta-analysis of studies evaluating the effects of CNIs in primary FSGS. They did not identify any trials in which CNIs were used as first-line treatment. Six randomized controlled trials and two retrospective cohort studies were included in their review. They performed a pooled analysis of the effect of cyclosporine on proteinuria remission; the relative risk of complete or partial remission was 7.0 (95% confidence interval (CI): 2.9, 16.8) compared with the control group.

It has been noted in treatment reviews that cyclosporine use in steroid-resistant patients is associated with a high relapse rate (e.g., 43% to 50% in a 2003 review by Cattran [22]). In an NIH-sponsored trial, FSGS-CT, 138 patients (adults and children) with biopsy-proven FSGS (assessed as steroid resistant and urine protein creatine ratio (UPCR) >1 g/g) were randomized to cyclosporine (n=72) or a combination of pulse dexamethasone (DEX) and mycophenolate mofetil (MMF) (n=66) [23,24]. Treatment was administered for 12 months and patients were followed until Week 78. Steroid resistance was defined as failure to achieve sustained UPCR ≤1.0 g/g after a minimal treatment duration of 4 weeks. All patients were treated with low-dose prednisone and either an ACEI or ARB. There was no difference between the groups in the primary endpoint (mean score of a 6-level categorical assessment of remission of proteinuria at Week 52): 46% of the CsA group and 33% of the MMF/DEX group had at least a partial remission at Week 52. In patients who achieved at least a partial remission at Week 52, relapse (defined as UPCR >2.0 g/g after the withdrawal of medication at Week 52) was reported for 33% (11/33) in the CsA group and 18% (4/22) in the MMF/DEX group. These data are difficult to interpret as 28% of patients in the CsA group had baseline UPCR <2.0 g/g. Moreover, the definition of steroid resistance in this study is not consistent with standard definition of steroid resistance for adults and the data are not presented separately for adults and children.

In a follow-up publication of a post-hoc analysis, Hogg et al [25] examined the outcomes in patients who achieved complete or partial remission after 26 weeks, completed 52 weeks of treatment, and had follow-up information through 78 weeks. In the cyclosporine group, the analysis included 22 of the 39 patients who were reported to have at least partial remission at Week 26 in the earlier publication, and 20 of the 26 patients in the MMF/DEX group. The authors report that, in the CsA patients, the mean eGFR decreased at Weeks 26 and 52 (17%

decrease and 19% decrease compared to baseline, respectively), and increased by 16% from Week 52 to Week 78.

There are few studies examining the use of tacrolimus in patients with FSGS. In one study [26], decrease in proteinuria was similar in 18 patients treated with cyclophosphamide/prednisone and 15 patients treated with tacrolimus/prednisone, both after 6 months of treatment and at the completion of a 6-month follow-up period. Baseline renal function was not recorded and there appeared to be stability of renal function between 6 months and 12 months. Therefore, it is difficult to assess the treatment benefit of tacrolimus from this study.

In summary, the available data, although largely from retrospective studies, support a treatment benefit of cyclosporine in steroid-resistant patients. There is little data supporting the benefit of cyclosporine as first line treatment. It has been reported that the relapse rate is high following discontinuation of treatment; however, it is difficult to interpret the data reported by Gipson et al [23,24] and Hogg et al [25] with respect to the effect of cyclosporine on renal function and proteinuria over 12 months and subsequent improvement in renal function and proteinuria after withdrawal, and the reported relapse rate. The study failed to recruit the target number of patients, the criteria for steroid resistance were not consistent with standard definitions, and the changes in proteinuria and renal function were not completely reported. However, it appears that there was a significant decrease in proteinuria at both Weeks 26 and 52. While the post-treatment effect on eGFR is not completely clear, the data suggest some increase in eGFR after withdrawal of treatment. The relevance of these findings to the long-term effect of voclosporin is not clear.

1.2.3 Voclosporin

Voclosporin is a next generation CNI currently under development for use in FSGS and lupus nephritis (LN). Voclosporin is structurally similar to 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 PK/PD predictability.

During the development of this investigational product, the legacy names of voclosporin, VCS, and ISA247 are referenced in discussions related to historical usage. In the Phase 3 LN clinical development program, the name of the investigational product is referred to as Orelvo, the proposed trade name. However, for the FSGS clinical development programs, the name of the investigational product will be referred to as voclosporin. All legacy names and the proposed trade name should all be considered interchangeable unless specifically identified as different.

Prior to the FSGS clinical development program, over 2,400 subjects have received investigational products containing voclosporin in 15 Phase 1, and 12 Phase 2/3 clinical studies in the indications of LN, transplant rejection, psoriasis and non-infectious uveitis. Detailed data for these clinical studies are presented in the IB [9].

1.2.3.1 Pharmacokinetic Considerations

Voclosporin approximates linear multiexponential PKs. Exposure to voclosporin was dose-related with maximum concentrations occurring ≤2 hours with a $t_{1/2}$ 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 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 C_{max} and an 18-fold increase in 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 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 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 Potential Toxicities of CNIs

Increased blood pressure (BP) and renal dysfunction are well known potential toxicities of CNIs that are dose-related, reversible, and generally responsive to dose reduction or temporary interruption of treatment [27].

Voclosporin has been studied in numerous disease states. In clinical studies of voclosporin in LN [9], a small proportion of voclosporin-treated subjects experienced an early drop of ≥30% in eGFR; however, that proportion then remained 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 treatment in 1 (1.1%) placebo subject, 7 (7.9%) voclosporin low-dose (23.7 mg BID) subjects and 5 (5.7%) voclosporin high-dose (39.5 mg BID) subjects. There were more TEAEs of hypertension seen in the voclosporin-treated subjects compared to placebo; however, overall mean systolic and diastolic 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 treatment.

There was also 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.

2. RATIONALE

The rationale for the development of voclosporin and the range of dose is to introduce a novel CNI to the population of patients with FSGS, with meaningful efficacy while minimizing toxicities common to other CNIs. In clinical studies, a favorable efficacy/safety profile for voclosporin has been demonstrated in the prevention of renal transplant rejection and in Phase 2 studies in LN.

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

The aim of the current study is to investigate whether voclosporin is able to reduce disease activity over a treatment period of 24 weeks. Subjects with histologic evidence of primary FSGS with proteinuria will be eligible to enter the study. Efficacy will be assessed by the ability of voclosporin to reduce the level of proteinuria (as measured by UPCR) while demonstrating an acceptable safety profile. The primary endpoint of this study will be complete or partial remission of proteinuria at 24 weeks.

2.1 Dose Rationale

This Phase 2 study is designed to initially evaluate the treatment benefit of voclosporin 23.7 mg BID in the first cohort of up to 10 subjects. The selection of this voclosporin dose for the first cohort (see Section 7, Study Treatments) was based on the previous experience with this drug in the Phase 2 LN study (AURA-LV). In AURA-LV, subjects were administered voclosporin 23.7 mg BID, voclosporin 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 ($p=0.045$). At Week 48, complete remission rates in both the low-dose (49.4%) and high-dose (39.8%) voclosporin groups demonstrated statistically significant superiority compared to the placebo (23.9%) group, ($p<0.001$, $p=0.026$, respectively). There was no increase in efficacy with the higher dose and no significant differences between the two voclosporin groups in achievement of renal response.

This study is also designed to evaluate a further dose level of voclosporin, this dose may be higher or lower than the initial 23.7 mg BID dosing. When the first 5-6 subjects in Cohort 1 have completed 12 weeks of treatment with voclosporin, the top line efficacy and safety data will be analyzed to determine the dose level for Cohort 2. The maximum dose possible for Cohort 2 will be 39.5 mg (5 capsules) BID. If the higher dose is selected for Cohort 2, subjects still receiving treatment in Cohort 1 may have their dose increased to 39.5 mg after Week 8 if they have not demonstrated meaningful benefit from the 23.7 mg BID dose per Investigator judgement and following discussion with the Medical Monitor. Subjects enrolled after the dose decision will receive voclosporin at 39.5 mg BID and be considered part of Cohort 2.

To minimize safety concerns, a cautious dose-escalation design starting with a minimal dose of one capsule (7.9 mg) per day will be employed for all subjects (see Section 7.1.2, Dosing Guidelines).

The protocol contains provisions for management of dose (including rules for stopping treatment with study mediation) based on safety concerns in particular, BP and renal function. The safety data from the use of voclosporin in LN demonstrates that these risks are dose-related, reversible, and can be managed by dose reduction and temporary interruption.

Furthermore, voclosporin will be administered as fixed doses 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, plaque psoriasis, and LN) demonstrated that weight did not have a significant effect on the PK of voclosporin [9].

3. STUDY OBJECTIVES

3.1 Primary Objective

- To assess the efficacy of voclosporin in achieving complete or partial remission of proteinuria after 24 weeks of therapy in subjects with FSGS.

3.2 Secondary Objective

- To assess the safety and tolerability of voclosporin over 24 weeks in subjects with FSGS.

3.3 Endpoints

All primary and secondary endpoints will be assessed overall and for each individual cohort.

3.3.1 Primary Endpoint

Proportion of subjects with remission of proteinuria at Week 24 based on the following parameters:

- Complete remission: UPCR of <0.3 mg/mg

  OR

- Partial remission: UPCR ≥0.3 mg/mg and <3.0 mg/mg with >50% reduction in UPCR from baseline

3.3.2 Secondary Endpoints

- Proportion of subjects with complete remission or partial remission of proteinuria at Weeks 8 and 12
- Proportion of subjects with complete remission of proteinuria at Weeks 8, 12, and 24
- Proportion of subjects with UPCR <0.5 mg/mg at Weeks 8, 12, and 24
- Proportion of subjects with partial remission of proteinuria at Weeks 8, 12, and 24
- Time to first occurrence of complete or partial remission of proteinuria
- Time to first occurrence of complete remission of proteinuria
- Time to first occurrence of partial remission of proteinuria
- Time to first occurrence of 50% reduction in UPCR from baseline
- Duration of UPCR <0.3 mg/mg

- Change from baseline in UPCR at each time point
- Proportion of subjects with a confirmed >30% decrease from baseline in eGFR (utilizing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula) at each time point
- Proportion of subjects with a confirmed >30% increase in eGFR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10)
- Change in UPCR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10)
- Change in eGFR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10)
- Change from baseline in serum creatinine, serum albumin, and eGFR at each time point
- Quality of life (QoL) assessments
  - Mean change in Patient Reported Outcome Measurement Information System (PROMIS) measures at Week 24
  - Change from baseline in Kidney Disease Quality of Life-Short Form (KDQOL-SF^{TM}) score at Week 24
- Safety and tolerability over 24 weeks
- Renal biopsy: descriptive analyses of changes in histopathology will be evaluated in post-treatment (24 weeks) renal biopsies in a subset of patients
- Change from baseline to Week 4 and 24 in the following biomarkers:
  - Urine nephrin
  - Urine synaptopodin
  - Serum TGF-β

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 2, open-label, multicenter, prospective, 24-week, exploratory cohort study to assess the efficacy and safety of two dose levels of voclosporin in achieving complete or partial remission of proteinuria in subjects with biopsy-confirmed primary FSGS. Subjects who have provided a signed and dated informed consent will be screened into the study. Subjects will be assigned a unique subject number which will be used to identify them throughout the study. The duration of the screening period will be approximately 4 weeks to 10 weeks (allowing for visit windows (14±3 days) for each stability assessment) to ensure that subjects meet eligibility criteria, including renal disease stability assessments. If a subject has not had a renal biopsy within the 6-month (prior to screening) required timeframe for study eligibility, one may be performed to assess eligibility into the study, provided the subject has given consent and provided the results can be obtained and reviewed before baseline; biopsy results over 6 months prior to screening may be permitted following review with the Medical Monitor. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to receive treatment with voclosporin. Up to 10 subjects will be enrolled into Cohort 1, at a starting dose of 7.9 mg BID for Week 1, 15.8 mg BID for Week 2, and a target dose of 23.7 mg BID for Weeks 3 to 24. The first dose of study treatment should occur in the morning on Day 2, the day after dispensing. Subjects will be contacted by telephone at the end of Week 1 and Week 2 to be reminded to increase their dose as per Section 7.1.2.1, Voclosporin Study Treatment.

Evaluable safety and tolerability from 12 weeks of treatment in the first 5-6 subjects from Cohort 1 are required in order to determine the dose level for Cohort 2. The dose selected may be higher or lower than 23.7 mg BID. The maximum dose possible for Cohort 2 will be 39.5 mg (5 capsules) BID. Dosing in this group will follow the same cautious approach as Cohort 1, with at a starting dose of 7.9 mg BID for Week 1, 15.8 mg BID for Week 2, 23.7 mg BID for Week 3 and a maximum dose of 39.5 mg BID for Weeks 4 to 24.

Doses and dose increments smaller than anticipated or an intermediate dose may be proposed for Cohort 2 based on the safety and tolerability results from the Cohort 1.

All subjects will return for assessment of efficacy and safety at Weeks 2, 4, 8, 12, 18, and 24. See Schedule of Events, for detailed information regarding visits.

All subjects, completed or withdrawn from the study, will complete the End of Treatment/Early Termination assessments (Visit 8) at Week 24, or at the time of withdrawal, and should attend two Safety Follow-up visits at 1 and 2 weeks after completion of treatment (i.e., at Week 25 (Visit 9) and Week 26 (Visit 10)) (or 7 and 14 days, respectively, following withdrawal) 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 up to 36 weeks. The duration of the screening period will be approximately 4 weeks to 10 weeks (allowing for visit windows) and the treatment duration is 24 weeks, with further Safety Follow-up visits at 1 and 2 weeks after last dose (completion or withdrawal).

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

5.1 Number of Subjects

It is anticipated that approximately 20 subjects will be recruited 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 years (or legal age of consent if >18 years) to 75 years of age, inclusive, at the time of consent.

3. Primary FSGS diagnosed by renal biopsy within 6 months prior to the screening visit. Biopsy results over 6 months prior to screening may be permitted following review with the Medical Monitor to confirm eligibility (see Appendix 3).

4. At initial screening assessment and at last qualifying assessment during screening period prior to baseline, FSGS subjects must have a urine protein creatinine ratio (UPCR) of ≥2.0 mg/mg. Subjects can be treatment-naïve or receiving steroid treatment (oral or intravenous (IV)) for FSGS. Subjects taking steroids must show signs of improvement in proteinuria, defined as at least a 20% improvement in UPCR from initiation of steroids to the last stability assessment prior to baseline. Subjects who have discontinued steroid treatment due to poor tolerability may be considered for the study. Subjects should also have a serum albumin level of ≤3.2 g/dL at screening and at the last qualifying assessment prior to baseline; subjects with serum albumin >3.2 g/dL may be included following review to confirm primary FSGS and after discussion with the Medical Monitor.

5. All subjects should be treated with ACEIs and/or ARBs unless they have documented intolerance or contraindication to these medications. Doses of these agents must be stable for at least 2 weeks prior to baseline, with BP ≤150/90 mmHg at the baseline visit (Visit 2).

    a) Subjects with nephrotic edema may be treated with diuretics during the screening period. Volume status should be optimized based on the clinical judgment of the Investigator and the doses of diuretics must be stable in the 2 weeks prior to baseline.

    b) At the discretion of the Investigator, subjects with hyperlipidemia may be treated with lipid-lowering agents (e.g., statins) in accordance with standard clinical practice. Doses must be stable in the 2 weeks prior to baseline.

6. Stable proteinuria, renal function, and BP during the 2 weeks prior to baseline, as assessed by the Investigator. Changes in UPCR, eGFR, and/or BP during the screening period may be due to treatments administered (e.g., ACEIs and ARBs); and, therefore, may interfere with study assessments or outcomes, or may place the subject at increased risk. All subjects must be discussed with the medical monitor prior to initiation of study treatment.

7. Women of childbearing potential must have a negative serum pregnancy test prior to dispensing study treatment. 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. Clinical or histologic evidence of secondary FSGS.

3. Histologic evidence of collapsing variant FSGS.

4. eGFR as calculated by the CKD-EPI equation of ≤30 mL/minute/1.73 m^2 at initial screening assessment or ≤45 mL/minute/1.73 m^2 at last qualifying assessment during screening period prior to baseline.

5. Currently taking or expected to require any of the prohibited medications listed in the protocol (see Section 7.6.1, Prohibited Medications) at screening or during the study. This includes prior use of cytotoxic or other immunosuppressant treatment for FSGS. Subjects who have discontinued steroid treatment due to lack of response are excluded from the study.

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

7. A previous renal transplant or planned renal transplant during the study.

8. Body mass index >40 kg/m^2 at last stability assessment.

9. Family history of nephrotic syndrome.

10. Any known hypersensitivity or contraindication to cyclosporine, or components of any cyclosporine drug product.

11. 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.

- Current or past 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.

12. Other clinically significant active medical conditions, such as:

- Severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome. Subjects with 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 are excluded.

- Liver dysfunction: aspartate aminotransferase, alanine aminotransferase, or bilirubin ≥2.5 times the upper limit of normal at last qualifying assessment during screening period prior to baseline.

- Chronic obstructive pulmonary disease or asthma requiring oral steroids.

- Bone marrow insufficiency: white blood cell count <2,500/mm^3, absolute neutrophil count <1.3 × $10^3/\mu L$, and/or thrombocytopenia (platelet count <50,000/mm^3) at screening or at last qualifying assessment during screening period prior to baseline.

- Current infection requiring IV antibiotics.

13. Any overlapping autoimmune condition for which the condition or the treatment of the condition may affect the study assessments or outcomes (e.g., any condition for which additional immunosuppression, including systemic corticosteroids, and/or cytotoxic therapy is indicated). Overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes are not excluded.

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

15. 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.

16. 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.

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

18. 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.

19. Subjects treated in a previous voclosporin clinical study.

5.4 Adequate/Effective Contraception

Women of childbearing potential must have a negative serum pregnancy test during 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, 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, reproductively competent men are required to use condoms during treatment and for at least 6 weeks after cessation of study treatment. In addition, female partners of male subjects are recommended to use an effective contraception during their partner's treatment and for at least 6 weeks after the last dose of study treatment. Male subjects are to refrain from making sperm donations during treatment and for at least 6 weeks after cessation of study treatment.

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.

Barrier methods (e.g., condoms, diaphragm, or cervical cap/sponge) when used alone are not considered highly 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 and documented 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 8), if possible. If possible, the subject should also be advised to come for the two Safety Follow-up visits (Visit 9 and Visit 10) at 1 and 2 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 withdrawal as "withdrawal of consent." Withdrawn subjects will not be replaced.

5.6 Discontinuation of Study Treatment

Discontinuation of study treatment does not necessarily constitute withdrawal from the study.

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.

If possible, subjects who are permanently discontinued from study treatment before the Week 24 visit should undergo all study assessments up to and including the Week 24 (or Early Termination Visit – Visit 8) and Safety Follow-up visits where appropriate. All subjects that discontinue study treatment should attend at least 2 further assessments after the last dose of study drug.

Guidance on when study treatment must be discontinued is in Section 7.4, Voclosporin Dose Modification.

5.6.1 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 discontinued 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 discontinued 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

Not applicable.

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 Pharmaceuticals Inc. (Aurinia).

7.1.1 Voclosporin – 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 Dosing Guidelines

7.1.2.1 Voclosporin

Voclosporin 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.

The dosing of voclosporin for Cohort 1 will be as follows:

- Week 1: 1 capsule (7.9 mg) orally (PO), BID
- Week 2: 2 capsules (15.8 mg) PO, BID

- Weeks 3 to 24: 3 capsules (23.7 mg) PO, BID

Evaluable safety and tolerability data from 12 weeks of treatment in the first 5-6 subjects from Cohort 1 are required in order to make the decision to escalate to a higher dose level for Cohort 2. The selected dose may be higher or lower than 23.7 mg BID. The maximum dose possible for Cohort 2 will be 39.5 mg (5 capsules) BID. Should this dose be selected the following dosing regimen will be followed:

- Week 1: 1 capsule (7.9 mg) PO, BID
- Week 2: 2 capsules (15.8 mg) PO, BID
- Week 3: 3 capsules (23.7 mg) PO, BID
- Weeks 4 to 24: 5 capsules (39.5 mg) PO, BID

All subjects will be contacted by telephone at the end of Week 1 and Week 2 (and Week 3, if applicable) to be reminded to increase their dose.

If the 39.5 mg dose is selected for Cohort 2, subjects still receiving treatment in Cohort 1 may have their dose increased to 39.5 mg BID after Week 8 per Investigator judgement and following discussion with the Medical Monitor.

All unused study treatment (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.

7.1.2.2 Corticosteroids

Subjects entering the study with corticosteroids should have their steroid dose gradually titrated down until they achieve a daily dose of <10 mg/day prednisone by Week 12. The timing of the titration is at the discretion of the investigator, with a reduction of 5 mg/day every 2 weeks recommended. If clinically indicated, steroid tapering may start during the stability assessment period. A dose level may be maintained for up to 4 weeks or increased per investigator judgement following discussion with the Medical Monitor. Refer to Appendix 4 for a conversion table of various formulations of steroids.

Corticosteroid treatment must be documented in the eCRF and source documentation.

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

Corticosteroids should not be re-started in a patient whose dose has been reduced to zero, or initiated during the study in treatment-naïve patients, without prior discussion with the Medical Monitor.

7.2 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.

7.3 Site Supply, Storage, Accountability

7.3.1 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.

7.3.2 Storage

Voclosporin softgel 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.

7.3.3 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, one 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's approval of the process and forward the certificate of destruction to Aurinia.

7.4 Voclosporin Dose Modification

7.4.1 Discontinuation of Study Therapy Due to Non-response

During the treatment period, any case where the subject experiences a worsening of proteinuria, or no improvement in proteinuria from baseline, once the highest permitted dose of study drug has been achieved, should be discussed with the Medical Monitor. Subjects may be allowed to add treatment with corticosteroids (IV or oral) while continuing with study drug, or may be discontinued from study treatment and transitioned to standard of care treatment.

If the dose level of 39.5 mg BID is determined for Cohort 2, any subject still on treatment in Cohort 1 who has completed 8 weeks of treatment and shown no meaningful improvement in proteinuria may have their dose increased to 39.5 mg BID per Investigator judgement and following discussion with the Medical Monitor.

7.4.2 Deterioration in Renal Function

Serum creatinine and eGFR utilizing the CKD-EPI formula, as reported by the central laboratory, will be used for the assessment of renal function at every visit including unscheduled visits.

It is recognized that eGFR may be unreliable at higher values (>100 mL/min/1.73 m^2). FSGS 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 [28], with or without kidney damage.

7.4.2.1 Decrease in eGFR >30% and eGFR <90 mL/min/1.73 m^2

During the treatment period, any subject experiencing a >30% decrease in eGFR from baseline (baseline eGFR is defined as the last assessment prior to first dose of study treatment) to <90 mL/min/1.73 m^2 will have study treatment interrupted until a repeat test can be performed (unscheduled visit to be completed within 48 hours). If the decrease is confirmed at the

unscheduled visit and not due to potential contributing factors (e.g., high baseline eGFR, the addition or modification of non-steroidal anti-inflammatory drugs (NSAIDs), ACEIs, ARBs, a concurrent state of dehydration, overdosing with study treatment, renal flare, etc.), the case should be discussed with the Medical Monitor, the study treatment should continue to be withheld, and eGFR retested within 48 hours. (Note: doses of ACEIs, ARBs, diuretics, and/or lipid lowering therapy are to remain stable throughout the study.) 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.

7.4.2.2 Decrease in eGFR ≤30% and eGFR <90 mL/min/1.73 m^2

During the treatment period, any subject having a ≤30% reduction in eGFR to <90 mL/min/1.73 m^2 should have the influence of potential contributing factors (as described in Section 7.4.2.1, Decrease in eGFR >30% and eGFR <90 mL/min/1.73 m^2) ruled out and appropriate corrective action taken. Any subject having a >20 to ≤30% reduction compared to baseline in eGFR to <90 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 should 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.

7.4.2.3 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.

7.5 Procedures for Overdose

Based on clinical experience with voclosporin, 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.

7.6 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.

7.6.1 Prohibited Medications

The following medications cannot be taking during the study:

- Cytotoxic or other systemic immunosuppressants
- Initiation of new treatment or change in dosage of ARBs and/or ACE inhibitors within 2 weeks prior to baseline
- Vaccines using live organisms, viral or bacterial
- 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 6 contains a summary of additional treatment and food restrictions.

7.6.2 Allowed Concomitant Medications

These medications are permitted during the study:

- Systemic corticosteroids as described in the Inclusion Criteria (see Section 5.2, Inclusion Criteria) and following the corticosteroid dosing guidelines (see Section 7.1.2.2, Corticosteroids)
- Doses of ACEIs and/or ARBs as described in the Inclusion Criteria (see Section 5.2, Inclusion Criteria)
- Doses of diuretics as described in the Inclusion Criteria (see Section 5.2, Inclusion Criteria)
- Doses of statins as described in the Inclusion Criteria (see Section 5.2, Inclusion Criteria)
- Topical steroids (e.g., nose, scalp, skin, inhaled)
- Herbal supplements can be used with caution and with approval by the Medical Monitor

Treatments which may be used as medically indicated, according to the judgment of the Investigator can be found in Appendix 5. 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 6.

7.7 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, the mean 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 withheld, an unscheduled visit arranged within 48 hours for repeat BP assessment, 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 [9].

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 (FMV) and from standard urinalysis results. If the FMV is for some reason not available at Day 1, Week 12 or Week 24, 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 (Table 1) will be drawn in accordance with the Schedule of Events.

Table 1 Review of Laboratory Assessments

Test Type	Test Parameters	Collection at Visits
Hematology	Complete blood count (CBC) 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)	All
	Differential (absolute and %) Bands Basophils Eosinophils Lymphocytes Monocytes Neutrophils	All

Test Type	Test Parameters	Collection at Visits
Coagulation	Coagulation Activated partial thromboplastin time (aPTT) Prothrombin time (PT) Partial thromboplastin time (PTT)	Screening
Blood Chemistry	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bicarbonate Bilirubin (direct and total) Blood urea nitrogen (BUN) Calcium Chloride	All
	Cholesterol (total, HDL, and LDL) & triglycerides Creatine kinase	Day 1 and Week 24
	Creatinine Gamma-glutamyl transferase (GGT) Glucose	All
	Glycosylated hemoglobin (HbA1c)	Day 1 and Week 24
	Lactic dehydrogenase (LDH) Magnesium	All
	Phosphorous, inorganic	Day 1 and Week 24
	Potassium Protein, total Sodium	All
Urinalysis and urine microscopy	Complete urinalysis (to include urine protein, creatinine, blood, urine microscopy).	All except for stability assessment visits during the screening period
FMV urine collection	FMV will be performed to analyze UPCR.	All
24-hour urine	UPCR	Day 1, Week 12 and Week 24 Note that 24-hour urine collection should be scheduled so as not to coincide with the FMV sampling due on the day of the study visit

Test Type	Test Parameters	Collection at Visits
Pregnancy Test	For females of childbearing potential.	Serum pregnancy test to be evaluated at central laboratory at Screening, and Week 24; urine pregnancy test will be performed locally at all other applicable visits.
Serology	Cytomegalovirus Hepatitis A, B, and C Hepatitis B surface antigen (HBsAg)	Screening (including stability assessments)
Special Tests	Estimated glomerular filtration rate (eGFR)	All
Biomarkers	Urine nephrin Urine synaptopodin Serum TGF-β	Day 1, Week 4 and Week 24

Notes: FMV = First morning void; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; UPCR = Urine protein creatinine ratio.

The total amount of blood that will be collected during the study from an individual subject is approximately 200 mL over 34 weeks.

For details on whether laboratory abnormalities should be reported as AEs and on the follow-up required in such cases, see Section 10.2.4, 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 FSGS-related manifestations which will also be recorded. A complete physical examination will be conducted at the initial screening assessment, 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.

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 heart rate (HR)
- Body temperature (°C or °F)
- Weight (kg)
- Height (cm)

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

At stability assessments, BP only will be included.

Height will be recorded at the initial screening assessment only.

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 mean BP measure is >130/80 mmHg (determined 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 7.7, 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 the initial screening assessment, Day 1, and Week 24.

9.1.4.1 Procedures to Manage a Treatment-Emergent Increase in QTcF

In the event that a subject has a corrected QT interval duration corrected for heart rate using method of Fridericia (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, study treatment will be discontinued and the subject followed until the QTcF value either returns to baseline 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 QoL Assessments

Assessments for QoL will be conducted at Day 1, Week 24, Week 25 and Week 26.

The PROMIS assesses physical function, pain interference, and fatigue. See Appendix 7.

The KDQOL-SF™ survey is a kidney disease-specific measure of QoL that assesses general health, kidney disease and its effects on daily life, and satisfaction with care. See Appendix 8.

9.1.6 Voclosporin Pharmacokinetic and Biomarker Assessment

Blood samples for PK assessments will be taken at Week 4 and Week 24. PK samples will be drawn prior to study treatment dosing (trough sample), and at 1, 2 and 4 hours post-dose. These samples will be analyzed for voclosporin. Should a subject experience a serious adverse event (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 treatment, further PK samples are not required.

Blood and urine samples for biomarker assessments will be taken at Day 1, Week 4 and Week 24, samples will be collected prior to study treatment dosing.

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 and Stability Assessment Procedures

The duration of the screening period will be approximately 4 weeks to 10 weeks (allowing for visit windows) and will consist of an initial screening assessment and 2 to 4 stability assessments to ensure that subjects meet eligibility criteria.

The initial screening assessment will include provision of informed consent; complete physical examination; medical history (including FSGS history); vital signs measurements, including weight and height; 12-lead ECG; blood and urine sample collection for central laboratory assessments, urinalysis, and urine microscopy; FMV urine collection (for determination of UPCR); a serum pregnancy test (for women of childbearing potential); and review of prior and concomitant medications and entry criteria. Following these assessments and if clinically indicated, subjects receiving steroids may start reducing their steroid dose as described in the corticosteroid dosing guidelines (see Section 7.1.2.2, Corticosteroids). Any AEs which occur after informed consent will be recorded.

Stability assessments will occur at 14-day intervals (±3 days) with the first assessment approximately 2 weeks after the initial screening assessment visit. Stability assessments 1 and 2 are mandatory; assessments 3 and 4 are optional if additional time is required for the subject's clinical status to stabilize. These stability assessment visits will include BP determination; blood sample collection for central laboratory assessments; FMV urine collection (for determination of UPCR); a serum pregnancy test (for women of childbearing potential); review of any AEs; and review of concomitant medications and entry criteria.

These renal disease stability assessments will be evaluated to ensure eligibility with respect to entry criteria for UPCR and eGFR.

Note that the laboratory assessments and FMV results of the last stability assessment will be used as the qualifying values for eligibility.

FMV urine samples (for determination of UPCR) will be collected at all visits during the screening period and must be returned and the results evaluated prior to Baseline/Day 1. If the FMV is for some reason not available at Day 1, Week 12 or Week 24, 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 samples will be drawn according to Table 1.

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 must have a negative serum pregnancy test result before baseline.

If a subject has not met the requirements in Inclusion Criteria #3 due to not having renal biopsy result within the required time frame, a renal biopsy can be performed as per local procedures, after signing the study consent, provided the results can be obtained and reviewed prior to baseline.

9.2.2 Treatment Procedures

Only subjects who meet all of the inclusion and none of the exclusion criteria will be eligible for study treatment.

Study medication will be dispensed per the Schedule of Events, beginning on Day 1. Subjects will take their first dose of study medication on Day 2. Women of childbearing potential must have a negative serum pregnancy test during Screening and a negative urine pregnancy test result on Day 1 prior to dispensing of study treatment.

Subjects in Cohort 1, will be contacted by telephone at the end of Week 1 as a reminder to increase their dose to 2 capsules (15.8 mg) BID for 1 week, starting at Week 2. Subjects will be contacted again by telephone at the end of Week 2 as a reminder to increase their dose to 3 capsules (23.7 mg) BID, starting at Week 3, for the remainder of the treatment period (see Section 7.1.2.1, Voclosporin).

Subjects in Cohort 2, will also be contacted by telephone at the end of each week, as required up to the end of Week 3, as a reminder to increase their dose of study medication to the maximum dose selected for the second cohort.

Subjects will complete all assessments per the Schedule of Events at Day 1 and at Weeks 2, 4, 8, 12 and 18.

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:

- PROMIS and KDQOL-SF™ QoL questionnaires will be answered by the subject, as first study procedure, at Day 1/Baseline.
- Abbreviated physical examination at Day 1.
- Vital signs including weight.
- Standard 12-lead ECG at Day 1.

- Blood and urine sample collection for analysis at central laboratory.
- FMV urine sample collection.
- Urine pregnancy testing at Day 1 (before dispensing study treatment)
- AEs.
- Concomitant medication.
- Returned capsule count and drug accountability (except Day 1).

9.2.3 End of Study (or Early Termination) Procedures

On completion of treatment at Week 24 or earlier if subject is withdrawn, all assessments for Visit 8 (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:

- PROMIS and KDQOL-SF™ QoL
- Abbreviated physical examination
- Vital signs including weight
- Standard 12-lead ECG
- Blood and urine sample collection for analysis at central laboratory
- FMV urine sample collection
- Serum pregnancy testing
- Pharmacokinetic and biomarker sampling
- AEs
- Concomitant medication
- Returned capsule count and drug accountability
- Repeat renal biopsy may be performed on a subset of patients

- Confirmation of completion/discontinuation

9.2.4 Follow-up Procedures

All subjects who complete the study or withdraw before Week 24 will be followed up at 1 week (±3 days) and 2 weeks (±3 days) after their last study treatment dose to collect any new AEs and concomitant medications. These 2 visits (Visit 9 and Visit 10) will be conducted as in-clinic visits.

Assessments for the follow-up visit are as follows:

- PROMIS and KDQOL-SF™ QoL
- Vital signs including weight
- Blood and urine sample collection for analysis at central laboratory
- FMV urine sample collection
- Concomitant medication
- AEs
- Confirmation of completed follow-up visit

9.2.5 Unscheduled Visit

Unscheduled visits may be performed during the course of the study for safety reasons. . Only the data relevant to the purpose of the visit will be collected in the source documents and eCRF. Additionally, unscheduled visits will be registered in the electronic data capture (EDC) system.

An unscheduled visit is requested in the following cases:

- After dose reduction at any time during the study (unscheduled visit within 2 weeks)
- QTcF value exceeding 500 msec, or an increase >60 msec from baseline, where the ECG will be repeated (confirmed) at an unscheduled visit within 24 hours
- Decrease in eGFR >30% compared to baseline (unscheduled visit within 48 hours), or a decrease in eGFR >20-30% compared to baseline (unscheduled visit within approximately 2 weeks)
- Symptomatic hypertension: Systolic BP is ≥165 mmHg or diastolic BP is ≥105 mmHg with symptoms of hypertension, see Section 7.7, Increased Blood Pressure (unscheduled visit within 48 hours)

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 one 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 events will also usually be considered serious.

Hospitalizations that have been scheduled prior to the subject signing the informed consent form (ICF), although not recorded as SAEs, must be documented in the subject's source documents. A renal biopsy performed as part of the study to verify eligibility will not be considered an SAE. Any complication experienced during a renal 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 ability to function. 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 treatment 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 treatment 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 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.

10.2.5 Abuse, Misuse, Overdose and Medication Error

All AEs of special interest such as study drug 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 observed from time of signing of the ICF will be recorded in the subject's source documentation. This applies to all AEs regardless of presumed relationship to the study drug. For screen failure subjects, any AEs and SAEs occurring during the screening period (after informed consent) will be recorded in the subject's source documentation only and will not be collected on the eCRF. Adverse events leading to discontinuation of study drug must be collected.

If any AE is reported, the date of onset, relationship to study treatment, relationship to disease under study, 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 one 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. Note that for screen failure subjects, any AEs and SAEs occurring during the screening period will be recorded in the subject's source documentation only. For enrolled subjects (i.e., those who successfully complete screening), the AE reporting period ends at the second Safety Follow-up visit (Visit 10). 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

For screen failure subjects, any SAEs occurring during the screening period (after informed consent) will be recorded in the subject's source documentation only and will not be collected on the eCRF.

For enrolled subjects (i.e., those who successfully complete screening), 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 drug or relationship to disease under study. For enrolled subjects, all SAEs will be recorded in the AE section of the subject's eCRF and source documentation.

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].

If notification is made via email or fax, site staff must enter the SAE information into the 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, whichever is longer. No formal study visit is required but Investigators must report any SAEs that occur during this 30-day period using the SAE reporting form provided; these will be entered into the safety database only. 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 or relationship to disease under study, 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 9) 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 drug-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 Institutional Review Board (IRB)/Ethics Committee (EC)/Independent Ethics Committee (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.

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

Not applicable.

12. DATA AND SAFETY MONITORING BOARD PROCEDURES

Not applicable.

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 approximately 20 subjects, with up to 10 subjects in Cohort 1 and at least 10 subjects in Cohort 2.

As this is an exploratory study, sample size calculations are not required. Descriptive statistics will be used and the results will only be hypothesis-generating.

13.3 Populations

13.3.1 Intent-to-Treat Set

The intent-to-treat (ITT) set will consist of all enrolled subjects (non-screening failures) and will be used for all efficacy analyses.

13.3.2 Safety Set

The safety set will consist of all subjects who have taken at least 1 dose of study treatment.

13.3.3 Per-protocol Set

The per-protocol set (PPS) will consist of all subjects eligible from the ITT set who do not have any major protocol violations. Major protocol violations will be defined in the SAP.

13.4 Datasets

Assessments taken at each visit will be analyzed using 2 different datasets. The first will be the observed cases dataset whereby all values collected will contribute to the dataset. A second dataset will be used for summaries and analyses incorporating data carried forward from a subject's last known value. This dataset will be referred to as the last observation carried forward dataset and as such, all subjects with any post-baseline efficacy assessment will contribute to the Week 24 analyses.

13.5 Background and Demographic Characteristics

Demographic and clinical disease characteristics will be summarized.

13.6 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, SD, median, minimum, and maximum) and frequency tables.

13.7 Concomitant Therapy

All concomitant medications will be coded by the World Health Organization Anatomical Therapeutic Chemical (ATC) Drug Reference List classification. The version used will be provided in the clinical study report.

13.8 Efficacy Evaluations

Primary and secondary endpoints will be assessed overall and for each individual cohort.

13.8.1 Primary Endpoint

The primary endpoint is the proportion of subjects with remission of proteinuria at Week 24 based on the following parameters:

- Complete remission: UPCR of <0.3 mg/mg

  OR

- Partial remission: UPCR ≥0.3 mg/mg and <3.0 mg/mg with >50% reduction in UPCR from baseline

13.8.2 Secondary Endpoints

The following are defined as secondary endpoints:

- Proportion of subjects with complete remission or partial remission of proteinuria at Weeks 8 and 12
- Proportion of subjects with complete remission of proteinuria at Weeks 8, 12, and 24
- Proportion of subjects with UPCR <0.5 mg/mg at Weeks 8, 12, and 24
- Proportion of subjects with partial remission of proteinuria at Weeks 8, 12, and 24
- Time to first occurrence of complete or partial remission of proteinuria
- Time to first occurrence of complete remission of proteinuria

- Time to first occurrence of partial remission of proteinuria
- Time to first occurrence of 50% reduction in UPCR from baseline
- Duration of UPCR <0.3 mg/mg
- Change from baseline in UPCR at each time point
- Proportion of subjects with a confirmed >30% decrease from baseline in eGFR (utilizing the CKD-EPI formula) at each time point (Baseline eGFR is defined as the last assessment prior to first dose of study treatment)
- Proportion of subjects with a confirmed >30% increase in eGFR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10)
- Change in UPCR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10)
- Change in eGFR from the final visit (Week 24 or last on-treatment visit, for subjects who discontinue prematurely) to the second Safety Follow-up visit (Visit 10)
- Change from baseline in serum creatinine, serum albumin, and eGFR at each time point
- QoL assessments
  - Mean change in PROMIS measures at Week 24
  - Change from baseline in KDQOL-SF^{TM} score at Week 24
- Safety and tolerability over 24 weeks
- Renal biopsy: descriptive analyses of changes in histopathology will be evaluated in post-treatment (24 weeks) renal biopsies in a subset of patients
- Change from baseline to Week 4 and 24 in the following biomarkers:
  - Urine nephrin
  - Urine synaptopodin
  - Serum TGF-β

13.9 Statistical and Analytical Methods

All statistical analyses relating to the primary and secondary objectives will be undertaken at study closure and will incorporate all available data.

In order to aid dose decisions for Cohort 2, an analysis of the first 5 or 6 subjects in Cohort 1 will be undertaken once the 5th or 6th subject reaches Week 12.

Given the small sample size, all analyses will be descriptive in nature.

Binary remission endpoints will be summarized using counts and proportions while continuous data will be summarized using means, SDs, medians, minimums and maximums. Kaplan-Meier methodology will be used for the analysis of time-to endpoints. Confidence intervals for proportions may be calculated but it is recognized that such intervals, being based on 20 patients, will be very wide. As an example, the 95% Clopper-Pearson CI for a proportion of 30% based on 20 patients is (11.9%, 54.3%).

The analysis of the primary endpoint, complete or partial remission of proteinuria at Week 24, will be conducted on the ITT set and confirmed with the PPS (if applicable). Remission of proteinuria will be summarized and an exact 2-sided 95% CI for the remission rate will be calculated.

The analyses of the secondary endpoints will incorporate the use of 2-sided 95% CIs and are described below:

- Binary endpoints will be summarized using counts and proportions along with exact 2-sided 95% CIs.

- Endpoints measured as a time-to-event will be displayed using Kaplan-Meier methodology. Median time-to-event along with 2-sided 95% CIs will be displayed.

- Other endpoints will be summarized by visit. Absolute values and differences between baseline and each time point up to and including Week 24 will be summarized using means and 2-sided 95% CIs. Changes between last on treatment value and post treatment follow-up will also be summarized.

Given the nature of the study, additional exploratory analysis will be undertaken as appropriate. This may include the reporting of individual case studies.

13.10 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 visit, and as change from baseline.

Adverse events and diseases 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 and up until 14 days after last dose will be considered TEAEs, though all AEs after informed consent will be recorded. SAEs occurring at any time after informed consent and prior to first study medication will be listed.

All prior and concomitant medications will be summarized using preferred terms and ATC Level 2.

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.

13.11 Interim Analyses

There will be no full interim analysis.

13.12 Other Evaluations

13.12.1 Pharmacokinetics

Estimates of voclosporin 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 [28] and the ICH guidelines for GCP [29]. 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 IRB/EC/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. These 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) must agree 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 termination 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 [31]. 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 [32] 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.

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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 after the screening period (including stabilization visits) in this trial (see Section 7.6.1, 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 Classification of FSGS

The epidemiology, classification and pathogenesis of FSGS has been reviewed by Reiser et al, 2017 [33].

According to this review, FSGS "is a histologic lesion, rather than a specific disease entity, that is commonly found to underlie the nephrotic syndrome in adults and children, particularly in the United States, Brazil, and many other countries. FSGS is characterized by the presence of sclerosis in parts (segmental) of some (focal) glomeruli on light microscopic examination of a kidney biopsy specimen."

According to this review, FSGS can be classified into the following etiologies, based upon the known and/or postulated causes of this histologic pattern:

- "Primary or idiopathic FSGS, which most often presents with the nephrotic syndrome."
- "Secondary FSGS, which most often presents with non-nephrotic proteinuria and, commonly, some degree of renal insufficiency. This category most commonly refers to FSGS that develops as an adaptive response to glomerular hypertrophy or hyperfiltration. This includes disorders associated with a reduced renal mass and/or renal vasodilation, such as unilateral renal agenesis. In addition, a nonspecific pattern of secondary FSGS can result from scarring produced by a previous injury (due to a variety of conditions, including active IgA nephropathy, vasculitis, and LN). Other secondary causes of FSGS include drugs and toxins (including heroin, interferon, and pamidronate) and viral infections (particularly HIV)."
- "Genetic causes of FSGS, which may present early in childhood with massive proteinuria and nephrotic syndrome or in adolescence or adulthood with less massive proteinuria."

Biopsy and diagnosis: According to Reiser et al, "precise quantification of sclerotic glomeruli requires three-dimensional morphometric analysis of entire glomeruli and the examination of sufficient glomeruli to ensure that the biopsy specimen is representative of glomeruli in the whole kidney. Kidney biopsies with few glomeruli (i.e., fewer than 15) cannot confidently exclude the diagnosis of FSGS, and, due to sampling error, some cases will be misclassified as minimal change disease."

"In patients who are found to have a FSGS lesion by light microscopy, the following approach can be used to distinguish between those with primary and secondary FSGS:

- Patients who present with nephrotic syndrome (ie, urine protein excretion >3.5 g/day and hypoalbuminemia), who exhibit extensive foot process effacement (≥80 percent) on EM [electron microscopic] examination, and who have no identifiable risk factors associated with secondary FSGS (eg, viral infection, drugs) most likely have primary FSGS, although genetic forms of FSGS lesions cannot always be excluded with confidence. Thus, primary FSGS is always a diagnosis of exclusion.

- Patients who present with subnephrotic (ie, <3.5 g/day in an adult) or nephrotic-range proteinuria and a normal serum albumin concentration (ie, without nephrotic syndrome) and segmental foot process effacement (<80 percent) on EM [electron microscopic] examination most likely have secondary FSGS."

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 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.

- At the discretion of the Investigator, subjects with hyperlipidemia may be treated with lipid lowering agents (e.g., statins) in accordance with standard clinical practice. Doses must be stable in the 2 weeks prior to baseline.

- Subjects with nephrotic edema may be treated with diuretics during the screening period. Volume status should be optimized based on the clinical judgment of the Investigator and the doses of diuretics must be stable in the 2 weeks prior to baseline.

- ACEIs, ARBs, and aliskerin and other therapies are recommended, as per standard guidelines, but if used their dose must be stable throughout the study. Subjects receiving ACEIs or ARBs must be on a stable dose for at least 2 weeks prior to baseline.

- In the case of uncontrolled hypertension (systolic BP >165 mmHg or diastolic >105 mmHg on two 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 7.7, Increased Blood Pressure.

Appendix 6 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 voclosporin metabolism
ACEIs and ARBs	Stable dose for at least 2 weeks prior to baseline	Change or commencement prohibited	Interfere with primary endpoint assessment
Foods			
Grapefruit and grapefruit juice	24 hours	Prohibited	May affect the metabolism of voclosporin

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

Appendix 7 PROMIS QoL Assessment

The PROMIS QoL assessment includes three questionnaires:

- Physical Function – Short Form 10a (PROMIS® Item Bank v2.0)
- Fatigue – Short Form 8a (PROMIS® Item Bank v1.0)
- Pain Interference – Short Form 8a (PROMIS® Item Bank v1.0)

Appendix 8 KDQOL-SF™ QoL Assessment Version 1.3

Your Health
– and –
Well-Being

Kidney Disease and Quality of Life (KDQOL-SF™ 1.3)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Thank you for completing these questions!

Study of Quality of Life
For Patients on Dialysis

What is the purpose of the study?

This study is being carried out in cooperation with physicians and their patients. The purpose is to assess the quality of life of patients with kidney disease.

What will I be asked to do?

For this study, we want you to complete a survey today about your health, how you feel and your background.

Confidentiality of information?

We do not ask for your name. Your answers will be combined with those of other participants in reporting the findings of the study. Any information that would permit identification of you will be regarded as strictly confidential. In addition, all information collected will be used only for purposes of the study, and will not be disclosed or released for any other purpose without your prior consent.

How will participation benefit me?

The information you provide will tell us how you feel about your care and further understanding about the effects of medical care on the health of patients. This information will help to evaluate the care delivered.

Do I have to take part?

You do not have to fill out the survey and you can refuse to answer any question. Your decision to participate will not affect your opportunity to receive care.

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. **In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several blocks	☐ 1	☐ 2	☐ 3
i	Walking one block	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes ▼	No ▼
a Cut down the amount of time you spent on work or other activities	☐ 1	☐ 2
b Accomplished less than you would like	☐ 1	☐ 2
c Were limited in the kind of work or other activities	☐ 1	☐ 2
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes ▼	No ▼
a Cut down the amount of time you spent on work or other activities	☐ 1	☐ 2
b Accomplished less than you would like	☐ 1	☐ 2
c Didn't do work or other activities as carefully as usual	☐ 1	☐ 2

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a Did you feel full of pep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b Have you been a very nervous person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
h Have you been a happy person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. Please choose the answer that best describes how <u>true</u> or <u>false</u> each of the following statements is for you.

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Your Kidney Disease

12. How <u>true</u> or <u>false</u> is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

13. These questions are about how you feel and how things have been going during the <u>past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the <u>past 4 weeks</u>…

	None of the time ▼	A little of the time ▼	Some of the time ▼	A good bit of the time ▼	Most of the time ▼	All of the time ▼
a Did you isolate yourself from people around you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b Did you react slowly to things that were said or done?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c Did you act irritable toward those around you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d Did you have difficulty concentrating or thinking?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e Did you get along well with other people?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f Did you become confused?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

14. During the <u>past 4 weeks</u>, to what extent were you bothered by each of the following?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
		▼	▼	▼	▼	▼
a	Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j	Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
k	Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
l	(Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
m	(Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Effects of Kidney Disease on Your Daily Life

15. Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease <u>bother</u> you in each of the following areas?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
a	Fluid restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Dietary restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Being dependent on doctors and other medical staff?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The next three questions are personal and relate to your sexual activity, but your answers are important in understanding how kidney disease impacts on people's lives.

16. Have you had any sexual activity in the <u>past 4 weeks</u>?

(Circle One Number)

No .....1 → If no, please skip to Question 17

Yes 2

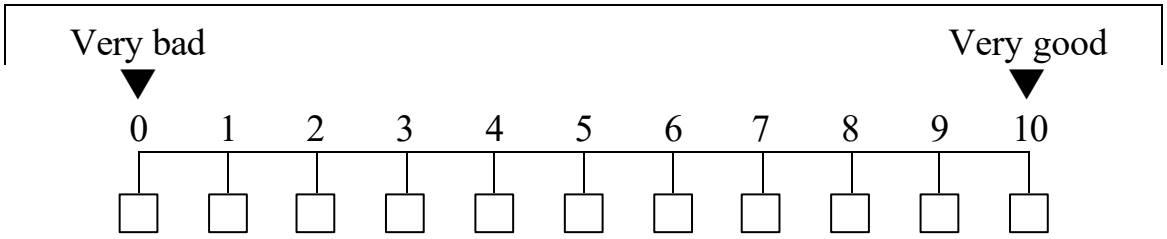
How much of a problem was each of the following in the <u>past 4 weeks</u>?

		Not a problem	A little problem	Somewhat of a problem	Very much a problem	Severe problem
		▼	▼	▼	▼	▼
a	Enjoying sex?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Becoming sexually aroused?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

17. For the following question, please rate your sleep using a scale ranging from 0 representing "very bad" to 10 representing "very good."

If you think your sleep is half-way between "very bad" and "very good," please mark the box under the number 5. If you think you sleep is one level better than 5, mark the box under 6. If you think your sleep is one level worse than 5, mark the box under 4 (and so on).

On a scale from 0 to 10, how would you rate your sleep overall? [Mark an ☒ in one box.]



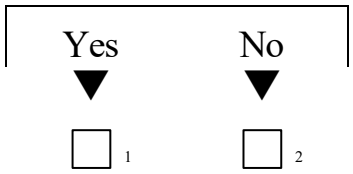
18. How often during the <u>past 4 weeks</u> did you...

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
	▼	▼	▼	▼	▼	▼
a Awaken during the night and have trouble falling asleep again?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b Get the amount of sleep you need?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c Have trouble staying awake during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

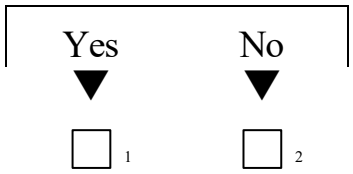
19. Concerning your <u>family and friends</u>, how satisfied are you with...

	Very dissatisfied	Somewhat dissatisfied	Somewhat satisfied	Very satisfied
	▼	▼	▼	▼
a The amount of time you are able to spend with your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4
b The support you receive from your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4

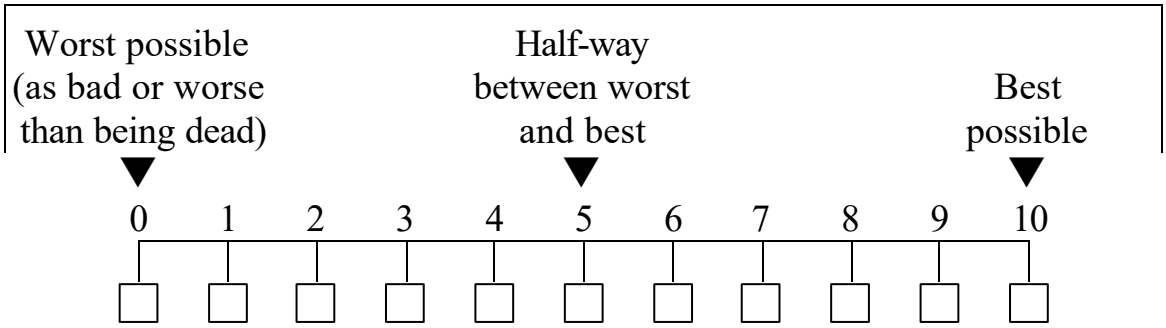
20. During the <u>past 4 weeks</u>, did you work at a paying job?



21. Does your health keep you from working at a paying job?



22. Overall, how would you rate your health?



Satisfaction With Care

23. Think about the care you receive for kidney dialysis. In terms of your satisfaction, how would you rate the friendliness and interest shown in you as a person?

Very poor	Poor	Fair	Good	Very good	Excellent	The Best
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

24. How <u>true</u> or <u>false</u> is each of the following statements?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a Dialysis staff encourage me to be as independent as possible	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Dialysis staff support me in coping with my kidney disease.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!