STATISTICAL ANALYSIS PLAN
AURORA 1 CLINICAL TRIAL
(AUR-VCS-2016-01)

Clinical Protocol Number:	AUR-VCS-2016-01
Study Name:	AURORA (AURinia Orelvo Renal Assessments) 1: Aurinia Renal Response in Active Lupus with Orelvo (voclosporin)
Study Title:	A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis
Date:	21st Oct 2019
Version:	V5.0
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AMENDMENTS BEFORE DATABASE LOCK

Version	Issue Date	Section	Revision/Addition	Rationale
2.0	*Jul 2018*	6.11.2.2 11	Adding additional covariate to the sensitivity analysis for the primary endpoint. Covariate will be MMF ≤2g versus MMF >2g. MMF dose to be defined as each patient's maximum dose during the study.	To assess possible differences between responses for patients taking higher levels of MMF.
2.0	*Jul 2018*	6.11.2.3 11	Component analysis for primary endpoint to be undertaken for both Adjudicated response and programmed response	To ensure full details of the analysis are available should differences between adjudicated response and programmed response become apparent.
2.0	*Jul 2018*	6.11.2.2 11	Sensitivity analysis using regional covariate will be defined at both continental and country level	To ensure sufficient information is available re: regional differences.
2.0	*Jul 2018*	6.11.3.3	Confirming Week 24 Renal Response will be a programmed endpoint only. This will not be adjudicated by the CEC	Ensuring consistency between the SAP and the CRC charter
2.0	*Sep 2018*	6.13.1	Updating assumptions for missing AE relationships	Ensure definitions are as per current requirements
2.0	*Sep 2018*	5 6.2.12 9	Confirming that region (used as blocking factor) will be in the primary model	Regulatory Agency feedback requesting clarification
2.0	*Sep 2018*	6.11.1	Adding clarification around the make-up of the CEC: blind and independent	Regulatory agency feedback
2.0	*Sep 2018*	6.11.1	Adding rescue medication clarifications	Regulatory Agency feedback
2.0	*Sep 2018*	6.11.2.1 6.11.2.2 6.11.2.3	Adding clarification around the sensitivity analyses, supplementary analyses and the tipping point analysis.	Regulatory agency feedback

2.0	*Sep 2018*	3.1	Clarifying that subjects who withdraw from the study are defined as non-responders	Regulatory Agency feedback
2.0	*Sep 2018*	3.2.1 3.2.2 9	Duration of UPCR ≤0.5 moved from key secondary to other secondary	Regulatory Agency feedback
2.0	*Sep 2018*	1	Clarification around IV methylprednisolone	Ensure consistency with protocol
2.0	*Sep 2018*	6.4	Clarification withdrawal versus discontinuation	Ensure consistent use throughout the SAP
2.0	*Sep 2018*	6.11.3.2 6.11.3.3 6.11.4.1 6.11.4.2 6.11.4.3 6.11.4.4	Referencing baseline section for endpoints that use non-standard calculations	Ensure baseline calculations are clear for each endpoint
2.0	*Sep 2018*	6.13.1	Add adverse event displays using exposure-adjusted incidence rates as a summary	Regulatory agency feedback
2.0	*Sep 2018*	6.13.1	Changing relative risk to risk difference in overall summary of AEs table	Retain consistency between treatment comparisons given the additional exposure adjusted summary tables
2.0	*Sep 2018*	Various	Consistently referring to 'population' rather than 'set'	Language consistency
3.0	*March 2019*	3.1	Paragraph added to detail the primary estimand	Regulatory agency feedback
3.0	*March 2019*	6.11.2.4	Step 3 updated to make it clear that stratification variables are to be included in the model and that different data is generated for each of the 50 analyses	Regulatory agency feedback
4.0	*May 2019*	6.11.2.4	Tipping point analysis: imputation model brought into line with the analysis model	Regulatory feedback
4.0	*May 2019*	Table 14.3.8.1 Section 6.13.1	Treatment Emergent Adverse Events by Descending Frequency of Preferred Term Safety Analysis Population	Added following review

4.0	*May 2019*	Table 14.3.8.2 Section 6.13.1	Non-Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Population	Added following review
4.0	*May 2019*	6.7 Medical History (Glossary 16.2.9.1) 6.8 Prior and Concomitant Medications (Glossary 16.2.9.2) 6.13.1 Adverse Events (Glossary 16.2.9.3)	Glossaries for medications, medical conditions and adverse events added	Added following review
5.0	*Oct 2019*	Section 6.2.2	Updated baseline definition for urine creatinine.	Updated following review
5.0	*Oct 2019*	Section 6.6	Added table for regions and countries in baseline comparability section.	Updated following review
5.0	*Oct 2019*	Section 6.7	Updated calculation of 'Years sinc …' variables.	Updated following review
5.0	*Oct 2019*	Section 6.11.2.3	Added clarifications for eGFR success.	Updated following review
5.0	*Oct 2019*	Section 6.13.1	Updated definition of TEAEs to be up to last dose + 30 days. Removed detailed list of AE tables and referring to list of tables instead.	Updated following review
5.0	*Oct 2019*	Section 11	Updated list of tables, listings and figures based on TFL review.	Updated following review
5.0	*Oct 2019*	Whole document	Finalization of the text throughout the document.	

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LIST OF ABBREVIATIONS

AE	Adverse event
AURORA	AURinia Orelvo Renal Assessments
Aurinia	Aurinia Pharmaceuticals Inc.
BID	Twice daily
BP	Blood pressure
C3 / C4	Complement 3 / complement 4
CEC	Clinical Endpoints Committee
CI	Confidence interval
dsDNA	anti-double-stranded deoxyribonucleic acid
EDC	Electronic data capture
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
HR	Heart rate
HRQoL	Health-related quality of life
ITT	Intent-to-treat
IV	Intravenous
IVC	Intravenous cyclophosphamide
IWRS	Interactive web response system
LN	Lupus nephritis
MMF	Mycophenolate mofetil
MMRM	Mixed Effect Model Repeated Measures
OR	Odds ratio
Orelvo	Voclosporin (for Phase 3 lupus nephritis indication)
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcF	QT interval duration corrected for heart rate using method of Fridericia
SAE	Serious adverse event
SAP	Statistical analysis plan
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
TEAE	Treatment-emergent adverse event
UPCR	Urine protein creatinine ratio
[redacted]	[redacted]

1 INTRODUCTION

This document details the planned statistical analyses for the AURORA, protocol "AUR-VCS-2016-01" study titled "A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis".

The proposed analyses are based on the contents of the final version of the protocol (Amendment 1 dated 04 May 2017).

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

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

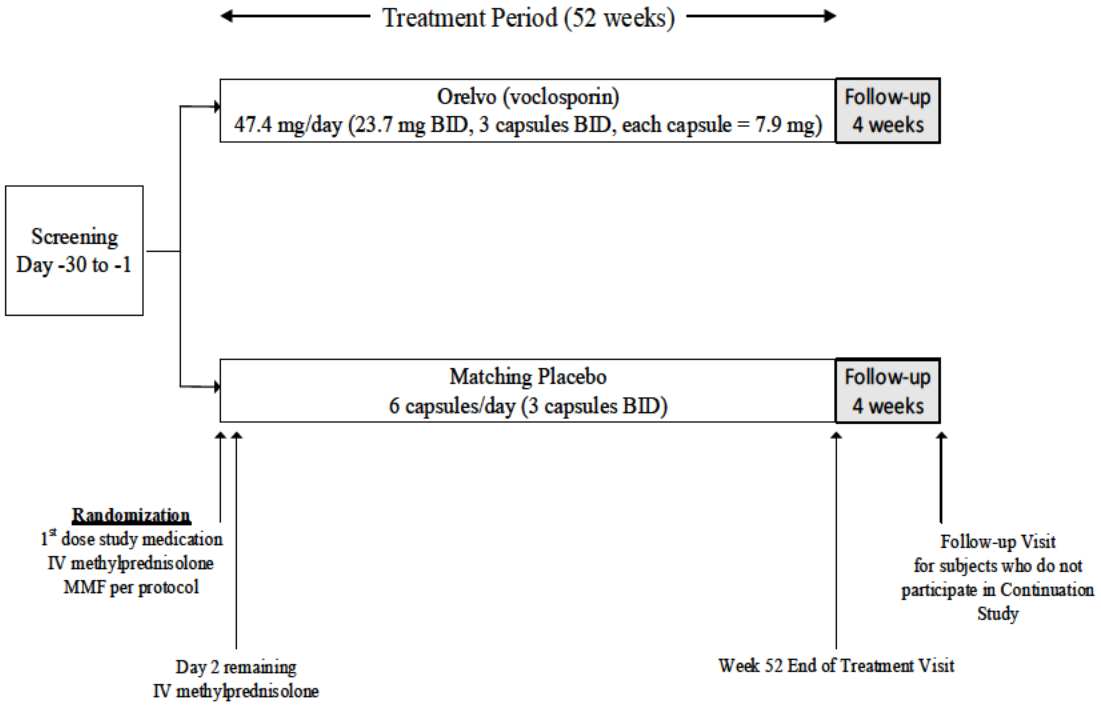
Baseline assessments will be performed before the first dose of study treatment is administered on Day 1. Using an interactive web response system (IWRS), eligible subjects will be randomized to receive either oral voclosporin 23.7 mg twice daily (BID) or matching placebo for 52 weeks. All subjects who weigh ≥45 kg should receive 0.5 g IV methylprednisolone on both Day 1 and Day 2 (a total of 1 g), before oral corticosteroid therapy is started on Day 3. All subjects who weigh <45 kg should receive 0.25 g IV methylprednisolone on both Day 1 and Day 2 (a total of 0.5 g). When subjects are receiving IV methylprednisolone, they should not receive oral corticosteroids on the same day. Starting at the Baseline Visit, all subjects will also receive background therapy with mycophenolate mofetil (MMF).

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

All subjects, completed or withdrawn, will complete the End of Treatment/Early Termination assessments (Visit 15) at Week 52 or at the time of early termination. Subjects who do not enroll in the planned continuation study will attend the Safety Follow-up Visit (Visit 16) at Week 56 to collect any new AEs and concomitant medications. At the follow-up visit, urine protein creatinine ration (UPCR) and estimated glomerular filtration rate (eGFR) will be assessed as well.

1.1 Schedule of Events

Figure 1.1 Schema



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

Table 1.1 AUR-VCS-2016-01 Schedule of Events

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

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

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

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

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

4 If a subject has not had a recent kidney biopsy, one may be performed to assess eligibility for the study provided informed consent has been given and results are received prior to randomization. If one is performed as part of standard of care after randomization, the results will be recorded in the electronic case report form.

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

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

7 Week 12 only.

8 Laboratory assessments will be performed according to the schedule in Section 6.13.2; subjects must be fasting for at least 8 to 12 hours at baseline and end of study/early termination.

9 Blood samples will be collected at 0 and 2 hours post dose on subjects who provide consent for pharmacokinetics.

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

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

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

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

14 For details on HRQoL assessments, see Section 6.11.4.8.

15 For details on Healthcare Resource Utilization, see Section 6.11.4.11.

16 Compliance only.

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

18 For subjects not on MMF during screening, will start receiving MMF therapy at the Baseline Visit and return for local complete blood count assessments at Weeks 1 and 3 after randomization.

19 IV methylprednisolone administered 0.5 g on baseline and Day 2. If IV corticosteroids must be administered during screening then the FMV urine specimens will be collected prior to the infusion.

Notes: Subjects who discontinue therapy will attend their regularly scheduled study visits to the end of the study. Subjects who withdraw consent and terminate the study early or discontinue treatment early should be advised to attend both Visit 17 and the Safety Follow up Visit (Visit 18).

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

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objective

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

3 ENDPOINTS

3.1 Primary Endpoint

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

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

The CEC will also take into account the following:

- Subjects who withdraw from the study prior to the Week 52 assessment and provide insufficient week 52 data to determine response will be defined as non-responders. Subjects who discontinue study drug but continue to attend study visits (as is the expectation) will have their data assessed for response.
- eGFR values eliminating a subject from complete remission should be accompanied by a treatment or disease-related treatment-emergent adverse event (TEAE) that impacts eGFR. Full details are given in Section 6.11.1.
- The CEC is independent and blinded from the treatment groups.

The primary endpoint estimand is the proportion of subjects showing renal response as adjudicated by the CEC in the ITT population when comparing voclosporin and placebo at Week 52. It is assessed in all randomized subjects who were recruited according to the inclusion/exclusion criteria of the protocol.

The variable is binary and indicates a response if a subject shows, at 1 year, adequate UPCR with no signs of detrimental impact on eGFR. Subjects who cannot be shown to be responders through their 1 year data (or absence thereof) are defined as non-responders.

Intercurrent events include:

- Treatment discontinuation for any reason
    - the subject remains on study, allowing the primary endpoint to be assessed at 1 year.
- Study discontinuation
    - resulting in insufficient information at 1 year to ascertain response status leading to assumed non-response.
- Rescue medication taken at any time prior to the primary assessment at 1 year
    - results in non-response. Rescue medication is adjudicated by the Clinical Endpoints Committee.
- Death at any time prior to the 1 year primary assessment
    - results in assumed non-response.

3.2 Secondary Endpoints

3.2.1 Key Secondary Endpoints

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

3.2.2 Other Secondary Endpoints

- Duration of UPCR ≤0.5 mg/mg
- Change from baseline in UPCR at each time point
- Change from baseline in serum creatinine, urine protein, and eGFR at each time point

- Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each time point
- Change from baseline in immunology parameters (complement 3 (C3), C4, and anti-double-stranded deoxyribonucleic acid (dsDNA)) at Weeks 24 and 52
- Renal response with low-dose steroids at Weeks 24 and 52 (defined as renal response in the presence of corticosteroids of ≤2.5 mg/day between Weeks 16 to 24 and Weeks 44 to 52)
- Change from baseline in health-related quality of life (HRQoL) at Weeks 12, 24, and 52
- Health Resource Utilization at Weeks 24 and 52
- Change from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity (SELENA-SLEDAI) Index score at Weeks 24 and 52

4 SAMPLE SIZE

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

- A two group continuity corrected Chi square test with a 0.05 two-sided significance level will have 80% power to detect the difference between a placebo response rate of 20.0% and a voclosporin response rate of 34.4% (odds ratio=2.1) when the sample size in each group is 162 (total N=324).

- The effect of withdrawals will be investigated. Subjects withdrawing for any reason will be counted as non-responders in the primary analysis and therefore no adjustment of sample size for withdrawals is necessary.

- The impact of withdrawals on primary endpoint will be investigated in the tipping point analysis.

Table 4.1 shows the voclosporin response rates required to maintain a minimum 80% power at the planned sample size for given placebo response rates. These response rates all lead to odds ratios of around 2, which is a clinically relevant effect.

Table 4.1 Voclosporin Response Rates Required to Maintain a Minimum 80% Power

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

5 RANDOMIZATION

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and subject names to enable records to be found at a later date. Subjects will be allocated a subject number at the screening visit and registered with an interactive central randomization system. Subjects meeting the required eligibility criteria will be randomized to treatment at Visit 2 (baseline).

The randomization will be stratified by biopsy class (Class V only versus Others) and by prior MMF use at time of screening. The subjects will be randomized in a ratio of 1:1 to receive either voclosporin 23.7 mg BID or matching placebo. To help ensure balance, a centralized randomization will be utilized where region will be employed as a blocking factor. This will ensure balance between treatment groups within each of the 4 regions: North America, Latin America, Europe / South Africa and Asia Pacific.

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Populations

Subjects excluded from the analysis populations and the reason for their exclusion will be listed in Appendix 16.2.

6.1.1 Screened Population

The Screened population includes all subjects who were screened and were allocated a subject number.

6.1.2 Intent-to-Treat Population

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

6.1.3 Per-Protocol Population

The Per-Protocol (PP) population will be a subset of the ITT consisting of those subjects who:

- Satisfy all of the inclusion / exclusion criteria
- Do not have any treatment administration errors
- Do not take prohibited concomitant medications

All protocol deviations will be assessed and documented on a case-by-case basis before the database lock and in a blinded fashion. Deviations considered to have a serious impact (major protocol violation) on the efficacy results will lead to the relevant subject being excluded from the PP population. Before database lock, potential subject exclusions from PP population will be reviewed by the Sponsor and documented in a subject evaluability document ([redacted]).

6.1.4 Safety Population

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

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

Except for parameters detailed later in this section, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug on Day 1. As assessments on day 1 are scheduled to be undertaken prior to taking study drug, day 1 assessments can be defined as baseline.

eGFR baseline will be calculated as the lowest measurement available prior to dosing.

Urine creatinine baseline will be calculated as the mean of the latest 2 pre-randomization values. Should only 1 value be available it will be used as the baseline value.

Urine protein baseline will be calculated as the mean of the latest 2 pre-randomization values. Should only 1 value be available it will be used as the baseline value.

UPCR values are calculated by the laboratory as the ratio of urine protein to creatinine. The ratio is only calculated where laboratory tests produce a result for both the creatinine and the protein. UPCR baseline will be calculated as the mean of the latest 2 pre-randomization values. Should only 1 value be available it will be used as the baseline value.

For the endpoints of change from baseline in UPCR and also for partial response endpoints (that incorporate a 50% reduction from baseline in UPCR), a second definition of baseline (alternative baseline) UPCR will be defined as the lowest measurement available prior to dosing.

6.2.3 Early Terminations Assessments

Data collected at Early Termination (ET) assessments will be mapped to the visits closest to the date of termination.

6.2.4 Duration/Study Day/Time

Study day will be calculated as the number of days from first dose of study drug (Day 1).

- Date of event – date of first dose of study drug + 1, for events on or after first dose
- Date of event – date of first dose of study drug, for events before first dose
- To this end, Day 0 remains undefined.

For all time to event analyses, subjects not reporting the specified endpoint will be censored at the time that the subjects were last known not to have experienced the endpoint. For all endpoints not encompassing death, all deaths will be treated as censoring events. In complex cases where the censoring time of the subject is uncertain, the case will be reviewed by the [redacted] statistician and a censoring time will be assigned and programmed prior to database lock.

6.2.5 Conventions for Missing and Partial Dates

All rules explained below for partial/missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

6.2.6 Missing/Partial Start/Stop Date of AEs and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows

<u>Partial or missing stop date will be imputed as follows:</u>

- If the stop date is completely missing and the event has resolved or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study.
- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.

- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.

- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the subject's screening date or the stop date of the event/concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.

- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.

- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

6.2.7 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing, then the date of last dose of study drug will be taken for analysis purposes as the date when the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed or the date of subject's last clinic visit in the study or early withdrawal or death whichever is earlier.

If only the month and year of the last dose was recorded, then the date of last dosing will be taken for analysis purposes as the date the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed, the last day of the month of the recorded last dose or the date of subject's last clinic visit in the study or early withdrawal or death whichever the earlier.

6.2.8 Missing Diagnosis Dates

If the month and year are present but the day is missing, the diagnosis date will be set to first day of the relevant month. If only the year is recorded the diagnosis date will be set as "01-Jan" for that year.

6.2.9 Exposure to Study Drug

Exposure to study drug will be calculated from the date of last dosing minus the first day of dosing + 1 for each prescribing record. Exposure will be summarized as the number of days on medication and mean daily dose. Mean daily dose will take into account periods where zero dose was prescribed.

6.2.10 Electrocardiogram Data

For ECG data recorded on continuous scales, if more than one value is recorded at a time point, the mean value rounded to the integer will be presented. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

6.2.11 Unscheduled Visits

All visits whether scheduled or unscheduled will be mapped to the closest scheduled protocol visit according to the protocol schedule of assessments. However, visits, when sorted by visit number and visit date, must remain in chronological order. In summary tables by visit, a subject's latest observation per visit will be tabulated. For assessments of continuous periods of remission, all available observations will be used.

All assessments will be listed in the relevant appendices to the CSR.

6.2.12 Randomization Strata

The randomization will be stratified by biopsy class (Class V only versus Others) and by prior MMF use at time of screening. A regional blocking factor will also be used for supply purposes ensuring balance within region. The stratification factors and the regional blocking factor will be used as covariates in the primary analyses.

6.2.13 eGFR

For the purposes of all eGFR summary tables and endpoints incorporating eGFR measures, an eGFR ceiling will be set at 90 mL/min/1.73m^2. In doing so, all values greater than 90 will be constrained to 90, thereby removing the reductions from renal hyperfiltration to normal renal function. These eGFR values will be labelled as 'Corrected eGFR'. Original, raw- eGFR measures will be displayed in listings. In addition, eGFR change from baseline tables will be produced using raw-eGFR values.

6.2.14 FMV and 24-Hour Urine

UPCR values will be determined using FMV urinalysis samples. In the event that the Investigator determines that the Screening, Week 24 or Week 52 FMV urinalysis sample was invalid, the UPCR values from the 24-hour urinalysis at the corresponding visit will be used instead of the FMV urinalysis in the calculation of efficacy endpoints. FMV analysis results will still be used for all other timepoints.

6.2.15 Adverse events

An AE with missing intensity of AE will be coded "Severe" which is the worst case. An AE with a missing relationship to Study Drug will be coded as "related". An AE with missing relationship to disease under Study will be coded as "related" to the disease unless the AE is recorded as being related to treatment.

6.3 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.3 or higher [1].

Summaries will be presented by treatment group or overall. Treatment group labels will be displayed as follows:

Placebo Voclosporin Overall

Overall columns are to be included within the table shells as follows:

Demography	Treatment and overall
Baseline	Treatment and overall
Disposition	Treatment and overall
Efficacy	Treatment
TEAEs	Treatment
Other safety	Treatment

Tables of events or medications will be ordered in descending frequency of subjects followed by (where applicable) events for the higher level term (system organ class or ATC levels 4 and 2) followed by the preferred term. Ordering will be for the VCS treatment group first followed by the placebo group and alphabetical thereafter.

Listings will be sorted in the following order treatment group, subject, parameter, and visit unless otherwise stated. All data will be listed, subjects who were not randomized will be displayed after the randomized treatment groups.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. For all tabulations of changes from baseline data, the lower and upper 95% confidence limits for the mean for the individual treatments will be given.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations out of the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1 Decimal Places

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

P-Values will be quoted to 3 decimal places. P-values < 0.001 will be presented as p<0.001.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects who entered the study, were randomized and who are in each analysis population will be summarized by treatment group and overall for the ITT population. This summary will be repeated for individual levels of the stratification and blocking variables. The reasons for exclusion from the Per-Protocol population will be summarized by treatment group and overall.

- The number of subjects who failed screening and the reasons for failure will be tabulated for all subjects. The number of subjects that were screened once, twice, 3 times, and total number of screened subjects will also be summarized.

- The number of early withdrawals and the reasons for withdrawals will be tabulated by treatment group and overall for the ITT population.

- The number of subjects that discontinue study drug will be presented by treatment group and visit for the ITT population.

- The number of subjects who complete Week 24, and those who complete Week 52 will be summarized for the ITT population.

- A summary of study drug discontinuation will be provided by visit for the ITT population.

6.5 Protocol Deviations

Major protocol deviations will be grouped into categories and summarized by treatment group and overall for the Safety and ITT populations. A listing of protocol deviations will be provided.

6.6 Baseline Comparability

The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented for the following variables based on the SS. Demography and disease history will also be summarized for the ITT and safety populations.

- Demographic data (summarized additionally by country and region for the Safety population)

- Disease history (including eGFR and UPCR measures)

- Medical/Surgical/ Systemic Lupus Erythematosus /Renal history

- Physical examination by body system at screening.

Regions and countries within regions are as follows:

Region	Country
Asia Pacific	Japan Korea (the Republic of) Malaysia Philippines (the) Thailand Taiwan (Province of China) Viet Nam
Europe + South Africa	Bulgaria Belarus Spain Croatia North Macedonia Netherlands (the) Poland Russian Federation (the) Serbia Turkey Ukraine South Africa
Latin America	Argentina Brazil Chile Colombia Costa Rica Dominican Republic (the) Guatemala Mexico Peru
North America	Canada United States of America (the)

6.7 Medical History

The results of the kidney biopsy will be summarized. Separate tabulations of previous and ongoing medical conditions, history of systemic lupus erythematosus (SLE) related conditions, and Renal (lupus nephritis) history collected at screening will be presented by treatment group and overall for the ITT and Safety. Conditions will be presented by Medical Dictionary of Regulatory Activities (MedDRA) primary system organ class and preferred term.

The summary of Lupus History summary for SLE involvement will include the following categories:

- Mucocutaneous

- Neurological
- Musculoskeletal
- Cardiorespiratory
- Vasculitis
- Hematology
- Antiphospholipid Syndrome
- Any other current SLE involvement to record (If 'Yes' it will be recorded)

For each of these categories, the following items will be summarized: Ever Involved (Yes/No), Currently Involved (Yes/No), years since onset.

The summary of the history of SLE related conditions will include the following categories:

- Diabetes Mellitus
- Hypertension
- Myocardial Infarction
- Stroke
- Deep Vein Thrombosis
- Hyperlipidemia

For each of these categories, both ever diagnosed and SLE related will be summarized.
Details of specific conditions falling into these categories will also appear in the General Medical History summary and treatments in the prior and/or concomitant medication summaries.

The number of years prior to baseline since diagnosis of the first occurrence of SLE will be summarized. For Renal History, the number of years prior to baseline since the 1st instance of a significant proteinuria (>500 mg/day), and the number of years prior to baseline since the first diagnosis of LN will be summarized as a continuous variable. Any previous dialysis (Yes/No),

and the number of years prior to baseline since the last dialysis will also be summarized. 'Years since…' variables will be calculated as year of informed consent – year of event + 1.

All data will be listed and a glossary of unique verbatim terms with coding information will be provided.

6.8 Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by treatment group and overall for the Safety population. Prior medications are defined as all medications starting and stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug. Medications will be summarized using ATC Level 2, 4, and preferred term.

The following previous LN therapies will also be summarized: MMF, IVC, Corticosteroids, Methotrexate, CNI, Biologic, Azathioprine, Antimalarial, other. The responses for these LN therapies are Yes or No.

All medications will be listed and a glossary of unique verbatim terms with coding information will be provided.

6.9 Exposure to Study Drugs

Overall exposure to study drugs (number of days of exposure to study drugs and mean dose) will be presented for both the Safety and ITT populations. Exposure will be based on prescribed dose. Exposure will not be summarized by visit but for the overall study duration. Overall study drug exposure will be calculated from the first dose date to the last dose date plus 1 for each prescribing record. Care should be taken to not double-count days. It is expected that prescription records will cover each study day between randomization and the end of study (or early termination). Periods of zero dose will be assigned as such.

The following gives an example of a subject with 4 prescription records over the 52-week (365 day) period.

Table 6.1 Exposure calculation example

Start Day	End Day	Dose (bid)	Duration
1	180	3	180 days
181	200	0	20 days
201	230	2	30 days
231	365	3	135 days

For the purposes of analysis this subject will have 'days on treatment' calculated as 180+30+135 = 345 days. Their mean daily dose will be:

(180*3 + 20*0 + 30*2 + 135*3) / 365 = 2.75 caps BID (converted to 43.45 mg per day).

Gaps between dosing records will be counted as a zero dose. For IV methylprednisolone, gaps between doses will not be taken into consideration.

For subjects who are lost to follow-up, and for whom the last dose date from the termination record is unknown, the date of the last available visit will be used as the last dose date.

Exposure to study drug will be summarized for the following:

- VCS/placebo
- MMF
- IV methylprednisolone
- Corticosteroids

Prescribed dose changes (Yes/No) at visit intervals and overall will be summarized for VCS/Placebo and for MMF.

6.10 Treatment Compliance

All unused study treatments (and any empty containers) dispensed to the subject will be returned at each study visit for capsule counts to check compliance. The Investigator will count the returned study treatment and this information will be used to assess subject compliance. Each subject is expected to take 6 capsules a day (47.4 mg/day, 23.7 mg BID, 3 capsules BID) with each softgel capsule = 7.9 mg. It should be noted that compliance will not be summarized by visit but for the overall study period.

Subject compliance with study drug (VCS / placebo) will be summarized by treatment group. Counts of the returned study treatment will be used to assess subject compliance. The study treatment count will be documented in the eCRF and source documentation.

Subject compliance will be calculated as:

$$\text{Compliance (\%)} = \frac{\text{number of dispensed capsules – number of returned or lost capsules}}{\text{number of prescribed capsules}} \text{ x } 100$$

The number of prescribed doses will be calculated as per the exposure calculation.

Compliance with the protocolled steroid taper will also be assessed and summarized. Subjects will be assessed as being either compliant or non-compliant.

6.11 Efficacy Analyses

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments will be reported with 95% confidence intervals for the odds ratio, hazard ratio or difference as applicable.

6.11.1 Primary Endpoint

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

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

The CEC will be blind to treatment group and completely independent of Aurinia. They will also take into consideration the following:

- Subjects who withdraw from the study prior to the Week 52 assessment and thus provide insufficient Week 52 data will be defined as non-responders
- Medication listings will be reviewed by the CEC as part of the adjudication process. The CEC will have complete autonomy to adjudicate any treatment as rescue medication. However, as any dose of MMF is permitted within this protocol there is no MMF dose level that necessarily classifies it as being rescue medication. As part of this review the CEC will also adjudicate on steroid drug use beyond the protocolled taper.

- eGFR values eliminating a subject from complete remission should be accompanied by a treatment or disease-related TEAE that impacts eGFR. To this end, eGFR measures which would ordinarily result in a subject not being in remission will only be used if the first eGFR assessment occurs on a date where there is also a treatment or disease-related, eGFR associated TEAE. The following is a list of MedDRA preferred terms that are associated with eGFR decreases:

    - BLOOD CREATININE INCREASED
    - CREATININE RENAL CLEARANCE DECREASED
    - GLOMERULAR FILTRATION RATE DECREASED
    - SERUM CREATININE INCREASED
    - RENAL IMPAIRMENT
    - RENAL FAILURE
    - RENAL FAILURE ACUTE

- Confirmation of eGFR decreases from baseline require that two consecutive measures at least 3 days apart exhibit the decrease.

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

H_0: There is no statistically significant difference in renal response between voclosporin and placebo at Week 52

H_1: There is a statistically significant difference in renal response between voclosporin and placebo at Week 52.

6.11.2 Primary Efficacy Analysis

6.11.2.1 Renal response at Week 52

Renal response at Week 52 will be adjudicated by the Clinical Endpoints Committee (CEC) and as such the analysis will incorporate the CEC's assessments of each subject. In order to perform their adjudication, the CEC will be provided UPCR data, eGFR data, steroid taper data, rescue and prohibited medication data and adverse event data. Full details of the adjudication process are detailed in a separate CEC Charter.

The primary efficacy analysis will be conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and renal response (Yes/No) at week 52 as the response variable (Table 14.2.1.1.2).

The results will be expressed as an odds ratio (and associated two sided- 95% CI) for voclosporin compared to placebo. Odds ratios greater than unity will mean the odds of response are greater for voclosporin than for placebo and therefore indicate a benefit of the voclosporin treatment arm. The p-value of the treatment effect will also be reported.

The following SAS program will be used for the primary efficacy analysis:

```
Proc Logistic data = data;
Class Treatment_arm MMF_Use Biopsy_Class Region;
Model Response = Treatment_arm MMF_Use Biopsy_Class Baseline_UPCR Region;
Run;
```

The number of responders and non-responders at Week 52 will be summarized by treatment arm and a listing of renal responders and non-responders will also be provided.

6.11.2.2 Sensitivity Analyses of the Primary Endpoint

The primary endpoint of adjudicated renal response at Week 52 in the ITT population will be analyzed using two different logistic regression models. The first sensitivity analysis will include only a term for treatment while the second sensitivity analysis will include terms for treatment, baseline UPCR, biopsy class and MMF use at baseline (i.e., omitting the regional covariate). Results will be reported in Table 14.2.1.2. The Odds ratios, 95% confidence intervals and p-values for voclosporin compared to placebo will be reported.

- The primary endpoint will also be analyzed, using the same ITT population, controlling in turn for each the following factors:
    - age (≤30 versus >30),
    - gender,
    - race (White, Asian, Other),
    - biopsy class,
    - region (defined at the continental level and, where numbers allow, country level),
    - MMF use at screening,
    - Maximum MMF Dose (≤2g versus >2g).

- An interaction between the factor and treatment group will be added to the model. A p-value for the main effect of the covariate in question along with the p-value for the interaction between treatment and covariate will be reported (Tables 14.2.1.7.1-7).

These sensitivity analyses will be performed on the same endpoint in the same population as set out in the primary analysis section; the only difference being the logistic models.

6.11.2.3 Supplementary Analyses based on the Primary Endpoint

A number of supplementary analyses based around the primary endpoint will be undertaken. Different aspects of the endpoint, be they the calculation method, different data assumptions or different populations will be varied to assess the impact of each.

- Renal response at Week 52 will be derived programmatically and analyzed in an identical fashion to the primary analysis (Table 14.2.1.1.2). Using the same definition as given to the CEC and as set out in the primary endpoint section, renal response at week 52 will be derived programmatically. All components of the primary response endpoint will be independently programmed apart from the use of rescue medication. The CEC adjudication on the use of rescue medication will be incorporated into the programmed endpoint.

- The analysis described in Section 6.11.2 will be repeated for the PPS (Table 14.2.1.3).

- The analysis described in Section 6.11.2 will be repeated for each biopsy class category (Class III, Class III/V, Class IV, Class IV/V, Class V and Class VI). The combining of classes may be necessary should subject numbers in any individual class be deemed insufficient. A separate category defined as "All but Pure Class V" will be defined (Table 14.2.1.4).

- For both the adjudicated week 52 renal response (primary endpoint) and the programmed week 52 renal response (supplementary endpoint), each individual component (and some component groups) of the endpoint will be summarized by treatment group and analyzed in the same manner using a logistic regression. Analysis will be undertaken where possible, however, it is recognized that individual components may include very low numbers of subjects (either responders or non-responders). "eGFR success" is defined as an eGFR measure of ≥60 mL/min/1.73 m^2 *or* no confirmed decrease from baseline in eGFR of >20% *or* no disease-related or treatment-related AE impacting eGFR. Where data allows, the numbers of subjects achieving each of the following will be summarized (Table 14.2.1.5.1 (adjudicated) and Table 14.2.1.5.2 (programmed)):

    - UPCR ≤0.5 mg/mg

- eGFR success
- UPCR ≤0.5 mg/mg and eGFR success
- Received no rescue medication for LN
- No withdrawal prior to remission assessment
- Did not receive more than 10 mg prednisone equivalent for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52, just prior to the renal response assessment

- "eGFR success" will also be summarized by individual components:
  - eGFR ≥60
  - eGFR <60 with no confirmed decrease >20%
  - eGFR <60 with confirmed decrease >20% but with no disease-related or treatment-related eGFR associated AE present at time of assessment.

  Confirmed decrease >20% in eGFR is two consecutive measurements, three or more days apart by the visit where response is defined.

6.11.2.4 Tipping point analysis for primary endpoint (CEC adjudicated Renal Response)

The impact of withdrawals on the primary endpoint will be investigated in a tipping point analysis where subjects whose response assessment was assumed due to missing data (missing data always results in a non-response assessment) will have their assessment re-assigned in a series of analyses that are progressively more in favor of placebo. Assuming that the primary analysis is significantly in favor of voclosporin, at some point, the series of analyses in the tipping point analysis is likely to show a lack of significance. It is of interest to assess how extreme the assumptions have to be around the subjects with missing data before primary significance is lost.

The tipping point analysis will consider the full range of possible response rates in the subjects with missing data in the primary analysis. This will be done by systematically changing assumed response rates from 0% to 100% in a stepwise manner. The imputation will be performed independently within the two treatment groups so that, in the most extreme case, the imputed response rate in the voclosporin arm will be 0% and 100% in the Placebo arm.

Multiple imputation will be used for each pair of response rates under consideration. Both the imputation model and the analysis model will incorporate the covariates as used in the primary analysis: Treatment arm, MMF use at screening, Biopsy Class, Baseline UPCR and Region. The combined results for each pair of response rates will be displayed graphically with the vertical axis being imputed placebo response (0 to 100%) and the horizontal axis being imputed voclosporin response (0 to 100%). Such a graph will be a comprehensive map of p-values using all plausible assumptions about missing outcomes and will provide a contour between significance and non-significance.

The following algorithm will be used for the imputation;

Step 1: Use efficacy data to identify subjects classed as non-responders due to missing data.

Step 2: 441 pairs of response rates for voclosporin and placebo in the table below will be used for the imputation.

Placebo Response Rate (Y)	**1**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	.95	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
	.9	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63
	.85	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
	.8	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105
	.75	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126
	.7	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147
	.65	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168
	.6	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189
	.55	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210
	.5	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231
	.45	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252
	.4	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273
	.35	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294
	.3	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315
	.25	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336
	.2	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357
	.15	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378
	.1	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399
	.05	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420
	0	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441
		0	**.05**	**.1**	**.15**	**.2**	**.25**	**.3**	**.35**	**.4**	**.45**	**.5**	**.55**	**.6**	**.65**	**.7**	**.75**	**.8**	**.85**	**.9**	**.95**	**1**
		Voclosporin Response Rate (X)																				

For each of the 441 pairs of response rates in the table above, (e.g., for pair number 255, response rate for voclosporin = 0.1, while response rate for placebo = 0.4.):

- For each subject identified in Step 1, generate a continuous response score between 0 (non-response) and 1 (response) using SAS proc mi adjusting for the covariates of treatment group, biopsy, MMF use at screening, baseline UPCR and region. Example SAS code is given below.
- Assign the imputed response (1 = response, 0 = non-response) based on the response score and the current tipping point. Using the example values above:
    - Given a voclosporin tipping point response rate of 0.1, subjects in the voclosporin group with a response score ≥0.9 would be imputed as responders and non-responders otherwise.
    - Given a placebo tipping point response rate of 0.4, subjects in the voclosporin group with a response score ≥0.6 would be imputed as responders and non-responders otherwise.

Example SAS code for the generation of a response score on the continuous scale (between 0 and 1):

```
proc mi data=impute01 out=impute20 nimpute=50 seed=3435 minimum=0 maximum=1;
      class TREATMENT BIOPSY MMF REGION;
      fcs nbiter=10 reg(RESPONSE = TREATMENT BIOPSY MMF UPCR REGION);
      var RESPONSE TREATMENT BIOPSY MMF UPCR REGION;
run;
```

For example, consider the case where 7 subjects (4 voclosporin, 3 placebo) in the data are considered non-responders due to missing data. Using the response rate number 299 (voclosporin = .2, placebo = .3)

Subject	Treatment	Continuous Response Score	Response Rate	Imputed Response
1	VCS	0.728119	.2	0
2	VCS	0.876749	.2	1
3	VCS	0.345234	.2	0
4	VCS	0.784817	.2	0
5	Placebo	0.923842	.3	1
6	Placebo	0.546724	.3	0
7	Placebo	0.734184	.3	1

Replace the response observed for the subjects in Step 1 (which, by definition, will be non-response) with their imputed data.

Step 3: Run the analysis of the primary endpoint (including stratification covariates) using the data in step 2. Repeat the imputation (step 2) and analyze 50 times to generate 50 individual odds ratios.

Step 4: Use Proc Mianalyze in SAS to pool the 50 odds ratios and output a common p-value.

Repeat Step 1 to 4 for all 441 pairs of response rates.

6.11.3 Key Secondary Endpoints

All the secondary efficacy analyses will be performed on the ITT population. The following key secondary endpoints will be analyzed. For all time to event analysis, estimates and 95% confidence

intervals of the 25th, 50th and 75th quantiles will be reported. The hazard ratio, 95% confidence interval, and p-value of voclosporin versus placebo will be reported. A Kaplan-Meier plot with both treatment arms will also be provided.

6.11.3.1 Time (weeks) to UPCR of ≤0.5 mg/mg

Time to UPCR of ≤0.5 mg/mg will be analyzed by comparing the survivor function between treatment arms. It will be estimated using Kaplan-Meier methodology and will be presented as a plot showing a line for each treatment group as well as the numbers remaining at risk for each treatment group at different time points. Median time to UPCR of ≤0.5 mg/mg along with two-sided confidence intervals will be displayed. Time to event will be measured as the number of weeks from day of randomization to the day of the event. Subjects who do not experience an event will be censored on the day of their last assessment of UPCR.

A Cox's proportional hazards model will be fitted to assess the significance of the differences between treatment arms. The model will include terms for treatment arm, baseline UPCR, biopsy class, MMF use at baseline and region. Estimates of the treatment effects will be expressed as hazard ratios (and associated 95% CI) for voclosporin relative to placebo. Hazard ratios greater than unity will indicate the hazard to be greater for voclosporin than for placebo and therefore indicate that the events in question generally occur earlier on active voclosporin and, for this endpoint, a benefit of voclosporin (Table 14.2.2). The log-log survivor function to proportional hazards will be assessed. A listing of time (weeks) to UPCR of ≤0.5 mg/mg responders and censors will be provided.

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

Change from baseline in UPCR will be calculated as the post baseline measurement minus the baseline measurement. Percent change from baseline will be calculated as:

- Percent change from baseline (UPCR_pc) = $\left(\frac{Change\ from\ baseline}{Baseline}\right)$ x 100

A 50% reduction in UPCR will be indicated by UPCR_pc ≤ -50. Subjects with missing UPCR_pc values will be considered non-responders. This endpoint will be analyzed and presented similarly to the primary efficacy endpoint as described in Section 6.11.2 (Table 14.2.3). A listing of subjects considered responders will be provided.

A supplementary analysis of partial response at both Week 24 and Week 52 will be undertaken using the alternative baseline definition (Section 6.2.2) of the lowest UPCR value pre-dosing.

6.11.3.3 Time to 50% reduction in UPCR from baseline

Time to 50% reduction in UPCR will be analyzed similarly to the end point described in Section 6.11.3.1. The definition and calculation of 50% reduction in UPCR is consistent with that described in Section 6.11.3.2 (Table 14.2.4). A listing of time (weeks) to a 50% reduction in UPCR, and censors will be provided.

A supplementary analysis of time to 50% reduction in UPCR will be undertaken using the alternative baseline definition (Section 6.2.2) of the lowest UPCR value pre-dosing.

6.11.3.4 Renal response at Week 24

- Renal response at Week 24 will be adjudicated by the CEC and also programmatically derived using similar definitions to those used to derive response at week 52. Steroid dosing will be assessed between weeks 16 and 24 and only rescue medication taken prior to the week 24 assessment will disqualify a subject from response.

- Renal response at week 24 (adjudicated and programmed) will be analyzed in a similar manner to that described in Section 6.11.2 (Table 14.2.5.1 and 14.2.5.2).

A listing of subjects with renal response at Week 24 will be provided.

6.11.4 Other Secondary Endpoints

The other Secondary endpoint analyses will be performed on the ITT population.

Change from baseline endpoints

Change from baseline in UPCR endpoints will be analyzed using a Mixed Effect Model Repeated Measures analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region and baseline UPCR included as a covariates in the model. Results will be expressed as differences between treatment arms (along with the associated 95% CI). The observed and change from baseline values will be summarized by treatment visit and treatment arms. The LS means and their corresponding 95% CI of the change from baseline values will also be presented for each visit and for the overall change. The model will be fitted using an unstructured (UN) covariance matrix. Should the UN covariance matrix not converge, then an autoregressive (AR(1)) covariance matrix will be used. The covariance matrix used will be indicated in the footnotes. The Kenward-Roger degree of freedom adjustment will be applied. LS mean plots of mean change from baseline versus visit will be presented for UPCR and eGFR.

The SAS code anticipated to be used for analysis of the change from baseline endpoints is as follows:

```
Proc Mixed data=dataset;
Class Treatment biopsy_class MMF_use Region visit subject;
Model response = Treatment biopsy_class MMF_use Region visit visit*treatment baseline/ DDFM=KR
Repeated Visit/subject =subject Type= UN R Corr;
LSmeans visit*treatment/PDIFF CL E;
Run;
```

6.11.4.1 Duration of UPCR ≤0.5 mg/mg

Duration of UPCR ≤0.5 mg/mg refers to the time (weeks) from the onset of the first UPCR ≤0.5 mg/mg to the subsequent, second occurrence of UPCR >0.5 mg/mg (i.e., allowing a single spike in UPCR). An event occurs at the time of the subsequent, second UPCR >0.5 mg/mg. Subjects who do not experience a subsequent, second UPCR >0.5 mg/mg will be censored at the date of the last UPCR assessment. Only subjects who achieved an initial response (UPCR ≤0.5 mg/mg) will be included in the analysis of this endpoint. Duration of UPCR ≤0.5 mg/mg will be analyzed in a similar manner to that described in Section 6.11.3.1 (Table 14.2.6).

An additional summary of this endpoint will be undertaken by summing the weeks between each UPCR measure ≤0.5 mg/mg and a subsequent measure >0.5 mg/mg. This will give an approximation of time spent with UPCR ≤0.5 mg/mg for each subject. This will be summarized and analyzed as a continuous endpoint and comparison between both treatment arms will be carried out using a 2 sample Wilcoxon test.

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

Percent eGFR change for a subject at a given visit will be calculated as:

- $\frac{\text{change from baseline}}{\text{Baseline}} x\ 100$

At any two consecutive time points, a subject that achieves a clinically significant >30% decrease in eGFR from baseline will be considered a confirmed eGFR drop subject at the earlier timepoint, otherwise they will be considered a non-eGFR drop subject. The proportion of subjects with a confirmed eGFR drop at each visit will be compared using the Chi Square or Fisher exact test if applicable. The proportion of eGFR drop subjects will be summarized at weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48 and 52 by treatment group. P-values of the differences at each visit will be reported (Table 14.2.7).

6.11.4.3 Change from baseline in UPCR at each time point

The response variable for the MMRM model will be the change from baseline in serum creatinine. Change from baseline in UPCR will be summarized at weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48 and 52 (Table 14.2.8.1). Listings of this endpoint will be provided with lab data. Baseline is calculated as defined in Section 6.2.2.

A supplementary analysis of change from baseline in UPCR will be undertaken using the alternative baseline definition (section 6.2.2) of the lowest UPCR value pre-dosing.

6.11.4.4 Change from baseline in serum creatinine

Serum creatinine data will be available in lab data. The response variable, change from baseline in serum creatinine, will be summarized at Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48 and 52 (Table 14.2.9). Listings of this endpoint will be provided with lab data. Baseline is calculated as defined in Section 6.2.2

6.11.4.5 Change from baseline in urine protein

Urine protein will also be collected from lab data. The response variable, change from baseline in urine protein will be summarized at Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48 and 52 (Table 14.2.10). Listings of this endpoint will be provided with lab data. Baseline is calculated as defined in Section 6.2.2.

6.11.4.6 Change from baseline in eGFR

Estimated glomerular filtration rate (eGFR) will be measured at all visits except Visit 2. The response variable change from baseline in eGFR will be summarized at Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48 and 52 (Table 14.2.11.1). Baseline is calculated as defined in Section 6.2.2.

These change from baseline tables will be produced using both corrected and raw eGFR values.

Listings of this endpoint will be provided with lab data.

6.11.4.7 Change from baseline in immunology parameters (C3, C4, and dsDNA) at Weeks 24 and 52

Each of the Lupus Markers: Complement 3, (C3), Complement 4 (C4), and dsDNA will be analyzed separately at weeks 24 and 52. C3, C4, and dsDNA is measured at screening, Week 24, and Week 52 (Table 14.2.12). Listings of this endpoint will be provided with lab data.

6.11.4.8 Renal response with low-dose steroids at weeks 24 and 52

Renal response with low-dose steroids is defined as renal response in the presence of corticosteroids of ≤2.5 mg/day between Weeks 16 to 24 (for Week 24 endpoint) and Weeks 44 to 52 (for Week 52 endpoint). This endpoint will be analyzed in a similar manner as that described in Section 6.11.2 (Table 14.2.13).

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

SF-36 and LupusPRO HRQoL will be answered by the subject at Baseline, Week 12, 24 and 52. Listings of observed and change from baseline HRQoL scores will be presented. A baseline HRQoL value is defined as the last HRQoL value prior to the first dose on Day 1. HRQoL total scores will be analyzed as a change from baseline endpoints described above for the ITT population.

6.11.4.9.1 Change from baseline in Short Form Health Survey (SF-36)

The SF-36 HRQoL assessment is a 36-question subject HRQoL questionnaire.The SF-36 responses will be weighted as indicated in Table 6.2.

Table 6.2 SF-36 responses and weighting

Item number	Original Response	Weight
1, 2, 20, 22, 34, 36	1 →	100
	2 →	75
	3 →	50
	4 →	25
	5 →	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1 →	0
	2 →	50
	3 →	100
13, 14, 15, 16, 17, 18, 19	1 →	0
	2 →	100
21, 23, 26, 27, 30	1 →	100
	2 →	80
	3 →	60
	4 →	40

Item number	Original Response	Weight
	5 →	20
	6 →	0
24, 25, 28, 29, 31	1 →	0
	2 →	20
	3 →	40
	4 →	60
	5 →	80
	6 →	100
32, 33, 35	1 →	0
	2 →	25
	3 →	50
	4 →	75
	5 →	100

These items will be further grouped into the following scales as shown in Table 6.3.

Table 6.3 SF-36 Scales

Scales	Number of items	Mean of Items
Physical functioning	10	3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Role limitations due to physical health	4	13, 14, 15, 16
Role limitations due to emotional problems	3	17, 18, 19
Energy/fatigue	4	23, 27, 29, 31
Emotional well-being	5	24, 25, 26, 28, 30
Social functioning	2	20, 32
Pain	2	21, 22
General health	5	1, 33, 34, 35, 36
Total mean score	36	All 36 items

Each scale will be calculated for each subject by taking the mean of its corresponding item. The observed and change from baseline scales values will be summarized by visit and treatment arm. Only the scales (Physical functioning, Role limitations due to physical health, Role limitations due to emotional problems, Energy/fatigue, Emotional well-being, Social functioning, Pain, General health, Total mean score) will be summarized (Table 14.2.14.1). An MMRM model of the change from baseline in total mean score will also be presented. The individual items and scales will be listed.

6.11.4.9.2 Change from baseline in LupusPRO(v1.7)

The LupusPRO (v1.7) is a 43-question subject HRQoL questionnaire specific for lupus. The questionnaire will be grouped into the following domains:

Table 6.4 LupusPRO questionnaire

Items	Construct	Domain	Reverse Coding needed?
1-3	HRQOL	Lupus Symptoms	Yes
4-5	HRQOL	Cognition	Yes
6-7	HRQOL	Lupus Medications	Yes
8-9	HRQOL	Procreation	Yes
10-14	HRQOL	Physical Health	Yes
15-19	HRQOL	Pain Vitality	Yes
20-25	HRQOL	Emotional Health	Yes
26-30	HRQOL	Body Image	Yes
31-34	N- HRQOL	Desires-Goals	Yes
35-36	N- HRQOL	Social support	No
37-39	N- HRQOL	Coping	No
40-43	N- HRQOL	Satisfaction with care	No

The LupusPRO© has 5 point Likert response format, where 0= None of the time/not applicable, 1= A little of the time, 2= Some of the time, 3=Most of the time, 4= All of the time, 5= Not applicable (recode as 0 for scoring). Reverse scoring for some items is required (as above). There are 12 observed domains. Item scores are totaled for each domain item and the mean domain score is obtained by dividing the total score by the number of items in that domain. The mean raw domain score is transformed to scores ranging from 0 (worst QOL) to 100 (best QOL) by dividing by 4 (the number of Likert responses {5 responses} minus 1) and then multiplying by 100, as below: (Mean raw domain score/4) x 100= Transformed score for the domain. Transformed domain scores will be obtainable when at least 50% of the items are answered. Total HRQOL and N-HRQOL scores are obtained by averaging the transformed domain scores within each construct. Observed and change from baseline values will be summarized by visit and treatment (Table 14.2.15). An

MMRM model of the change from baseline in HRQOL and N-HRQOL score will also be presented. A listing of the 43 items, the domains, and the total HRQOL and total N-HRQOL will be provided.

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

The SELENA-SLEDAI assesses disease activity within the last 10 days. Twenty-four items are scored for 9 organ systems, and summed to a maximum of 105 points. A score of 6 is considered clinically significant. Assessments for SELENA-SLEDAI will be conducted at baseline, Week 24, and Week 52. A patient's SELENA-SLEDAI total score at a given visit is the sum of the weighted scores of all marked SLE-related descriptors. A total score can fall between 0 and 105, with a higher score representing a more significant degree of disease activity. Change from baseline in SELENA-SLEDAI total score will be the response variable in the MMRM model (Table 14.2.16). The scores of the individual SELENA-SLEDAI items and the total score of each subject will be listed.

6.11.4.11 Health Resource Utilization at Weeks 24 and 52

Information on healthcare resource utilization will be collected at time points: baseline (Day 1), Week 24, and Week 52, and documented in the EDC system. This information will be collected via interview of the subject by the study staff and entered into the EDC system. General information collected may include:

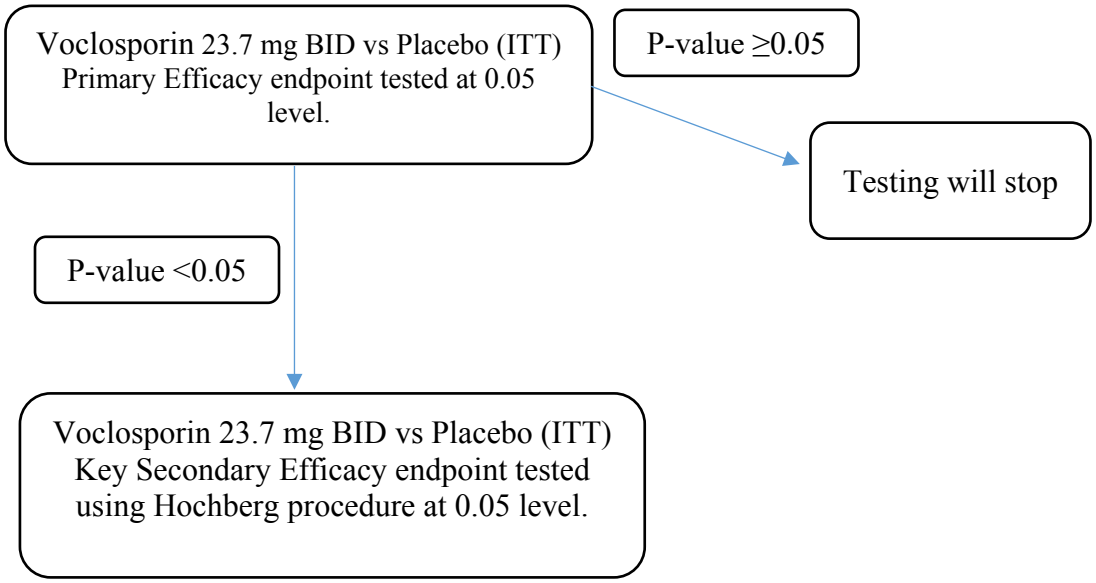
- Type of insurance coverage (private, NHS, other)
- Number of visits to ANY health care professionals (HCP), other than study doctor
- Types of HCP visited (specialists versus primary care)
- Time spent on visits (in minutes)
- Diagnostic tests performed (Yes/No)
- Time (in minutes) spent by caregivers assisting patient with HCP visits
- Prescriptions issued (Yes/No), filled (Yes/No)
- Community services used (Yes/No)

Each item in the Health Resource Utilization questionnaire will be summarized for baseline (Day 1), Week 24, and Week 52. All the items will also be listed at subject level.

6.11.5 Multiplicity

An overall type 1 (false-positive) error rate of 5% for the efficacy endpoints will be maintained so that no statistical significance for the key secondary efficacy endpoints will be claimed unless the principal analysis of the primary efficacy endpoint using the ITT population is statistically significant at the 5% level. The Hochberg step-up procedure [2] will be used to adjust for multiple comparisons amongst key secondary endpoints and maintain the overall type 1 error rate. Data from all analyses, regardless of the level of significance, will be presented for review.

Figure 6.1 Hochberg procedure



6.11.5.1 First Overall Comparison -Voclosporin 23.7 mg BID versus Placebo for Primary Efficacy Endpoint.

The comparison of voclosporin 23.7 mg BID versus Placebo in the primary efficacy endpoint, renal response at Week 52, will be tested first at a 0.05 significance level. If the p-value for this comparison ≥0.05, then testing will stop. Otherwise, the comparisons of voclosporin 23.7 mg BID versus Placebo for the Key secondary efficacy endpoints will be tested using the Hochberg procedure.

6.11.5.2 Secondary Comparisons - Voclosporin 23.7 mg BID versus Placebo for Secondary Efficacy Endpoint.

The key secondary endpoints are:

- Time to UPCR ≤0.5 mg/mg
- Partial renal response at Week 52
- Partial renal response at Week 24
- Time to 50% reduction from baseline in UPCR
- Renal response at Week 24 (Adjudicated)

If the testing proceeds to the comparison of voclosporin 23.7 mg BID versus Placebo treatment groups for the key secondary endpoints, then Hochberg testing procedure will be utilized. The p-values from the key secondary efficacy endpoints will be ordered from smallest to largest. The largest of these p-values will be compared to a significance level of 0.05. If the test rejects the null hypothesis of no treatment difference, then all p-values for the key secondary efficacy endpoints for voclosporin 23.7 mg BID versus Placebo treatment group will be declared statistically significant. If the largest p-value is not less than 0.05, then this p-value will not be declared statistically significant and testing will proceed to the next largest p-value.

If the largest p-value is not found to be statistically significant, then the second-largest p-value will be compared to a significance level of 0.05/2 = 0.025. If this p-value is less than 0.025, then this p-value and the remaining p-values will be declared to be statistically significant. If the second largest p-value is not less than 0.025, then this p-value will not be declared to be statistically significant and testing will proceed to the third largest p-value.

If the second largest p-value is not found to be statistically significant, then the third largest p-value will be compared to a significance level of 0.05/3 = 0.0167. If this p-value is less than 0.0167, then this p-value and the remaining p-values will be declared to be statistically significant. If the third largest p-value is not less than 0.0167, then this p-value will not be declared to be statistically significant and testing will proceed to the fourth largest p-value.

This process will continue until all p-values have been assessed as non-significant or significant.

6.12 Pharmacokinetic Analyses

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.

6.13 Safety Analyses

The safety analyses will be presented by the treatment received. The following safety endpoints will be summarized;

- 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

6.13.1 Adverse Events

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug up to last dose + 30 days. For subjects consenting to the AURORA 2 continuation study there will be an additional constraint to the TEAE definition: events must have an onset date prior to the first dose of AURORA 2 study drug.

A treatment-related TEAE is defined as a TEAE that is assessed by the Investigator or Sponsor as being related to study drug. If a TEAE has a missing relationship to study drug it is assumed to be related to the study drug for analysis purposes.

A disease-related TEAE is defined as a TEAE that is assessed by the Investigator or Sponsor as being related to the disease under study. If a TEAE has a missing relationship to the disease under study it is assumed to be related to the disease under study for analysis purposes.

Missing severity assessments will be summarised as severe.

The following tables will be presented for AEs:

- Summary table of overall incidence, the number of events, risk difference and 95% CI (voclosporin-placebo) including the following top line summaries:
    - Any AE
    - Any TEAE
    - Any Treatment-Related TEAE
    - Any Serious TEAE
    - Any Treatment-Related Serious TEAE
    - Any TEAE Leading to Voclosporin/Placebo Discontinuation
    - Any TEAE Leading to Death
    - Treatment-Related TEAE Leading to Death
    - Disease-Related TEAE
    - Disease-Related Serious TEAE

Detailed list of AE tables is given at the end of this SAP.

In counting the number of AEs reported, a continuous event (i.e., reported more than once and which did not cease), will be counted only once for a subject; a non-continuous AE reported several times by the same subject will be counted as multiple events.

Additional tables for serious TEAEs will be provided for each of the four regions: North America, Latin America, Europe/South Africa and Asia Pacific. Similar tables will also be provided for serious TEAEs occurring between day 1 and day 84 (Up to week 12), day 85 to day 168 (Week 12 to 24) and greater than day 168 (after week 24).

All AEs will be listed and a glossary of unique verbatim terms with coding information will be provided.

6.13.1.1 Exposure-adjusted incidence rates

Additional tables of exposure-adjusted incidence rates (EAIR) for certain groups of adverse events will be provided. The exposure for a given preferred term will be calculated for each treatment group as the total time at risk of an event. Each subject will have their exposure (t_i) calculated with the exposures being summed to generate an overall exposure (T) for the event in question for each treatment group. Exposures will be calculated differently depending on whether the subject did or did not experience the event in question.

For subjects experiencing the event in question exposure is calculated as the number of days from first dose of study drug to the time of the event.

For subjects not experiencing the event in question exposure is calculated as the number of days from first dose to the end of the study.

Incidence rates (IR) for each preferred term are calculated within treatment group as the number of subjects (n) experiencing the event divided by the total time at risk for all subjects in the treatment group. Exposure-adjusted incidence rates will be displayed as the number of events / 100 years of exposure. The difference (voclosporin minus placebo) between the exposure adjusted incidence rates along with a 95% CI for the difference will be reported for each preferred term using the normal approximation [3].

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

The test statistic is given by (v=voclosporin, p=placebo):

$$E = \left(\frac{n_v}{T_v} - \frac{n_p}{T_p}\right) \Big/ \sqrt{\frac{n_v}{T_v^2} + \frac{n_p}{T_p^2}}$$

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

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

Using exposure adjusted incidence rates, the following tables will be provided:

- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term using Exposure-Adjusted Incidence Rate [subjects (n), exposure and treatment comparisons]
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term using Exposure-Adjusted Incidence Rate [subjects (n), exposure and treatment comparisons]

6.13.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, urinalysis and serum chemistry

continuous parameter. Each measurement will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

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 table below shows the tests, parameters, and time points that will be summarized by treatment arm. For the screening time points, only the last non-missing measurements will be included in the summary.

Table 6.5 Laboratory Parameters

Test Type	Test Parameters	Time Points
Hematology	Complete blood count (CBC)	All except Day 2
	Hematocrit	
	Hemoglobin	
	Mean corpuscular hemoglobin (MCH)	
	Mean corpuscular hemoglobin concentration (MCHC)	
	Mean corpuscular volume (MCV)	
	Platelet count	
	Red blood cells (RBC)	
	Red blood cell morphology	
	White blood cells (WBC)	
	Differential (absolute and %)	All except Day 2
	Bands	
	Basophils	
	Eosinophils	
	Lymphocytes	
	Monocytes	
	Neutrophils	
	Erythrocyte sedimentation rate	Day 1, Week 24, and Week 52
Coagulation	Coagulation	Screening
	Activated partial thromboplastin time (aPTT)	
	Prothrombin time (PT)	
	Partial thromboplastin time (PTT)	

Test Type	Test Parameters	Time Points
Urinalysis	Complete urinalysis (to include urine protein, creatinine, blood, urine microscopy). First morning void will be performed to analyze urine protein/creatinine ratio. A 24-hour UPCR may be substituted for FMV at entry (or endpoint) if required.	All except Day 2
Pregnancy Test	A serum pregnancy test will be performed for females of childbearing potential. Urine pregnancy tests will be done using a dipstick.	Screening and Weeks 24 and 52 (Serum) All other applicable visits (Urine)
Serology	Cytomegalovirus	Screening
	Hepatitis A, B, and C	
	Hepatitis B surface antigen (HBsAg)	
Special Tests	Estimated glomerular filtration rate (eGFR)	All except Day 2
Blood Chemistry	Alanine aminotransferase (ALT)	All except Day 2
	Albumin	
	Alkaline phosphatase (ALP)	
	Aspartate aminotransferase (AST)	
	Bicarbonate	
	Bilirubin (direct and total)	
	Blood urea nitrogen (BUN)	
	Calcium	
	Chloride	
	Cholesterol (total, HDL, and LDL)	Day 1, Week 24, and Week 52
	Creatine kinase	Day 1, Week 24, and Week 52
	Creatinine	
	Gamma-glutamyl transferase (GGT)	
	Glucose	
	Glycosolated hemoglobin (HbA1c)	Day 1, Week 24, and Week 52
	Lactic dehydrogenase (LDH)	
	Magnesium	
	Phosphorous, inorganic	Day 1, Week 24, and Week 52
	Potassium	
	Protein, total	
	Sodium	
	Triglycerides	
	c-Reactive Protein	Screening, Week 24, and Week 52

A listing of all laboratory measurements recorded throughout the study will be presented.

6.13.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Body temperature (degrees Celsius)

Mean values for systolic and diastolic blood pressure will be used in the summary tables. Where the mean value is unavailable, an individual measure at the visit in question will be used. Listings of all vital sign measurements will be provided.

6.13.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables at screening, Week12, Week 24, and Week 52 will be tabulated at each follow-up:

- Heart rate (bpm)
- PR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms)
- QTcF interval (ms)

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) from baseline to each follow-up visit will be presented. Listings of all ECG measurements will be provided.

6.13.5 Physical Examination

Physical examination will be summarized for the safety population at timepoints: screening, Day 1 (Baseline), Week 24, and Week 52. The following parameters will be summarized: Height (as part of demography at screening only) and Weight.

Physical examination results with clinically significant abnormalities (Yes/No) will be listed.

7 INTERIM ANALYSIS

There are no planned interim analyses. The analysis of the primary endpoint (renal response at Week 52) will be conducted at the end of the study.

8 DATA AND SAFETY MONITORING BOARD ANALYSES

Data and Safety Monitoring Board (DSMB) analyses are detailed in a separate DSMB charter and associated documents.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

In the randomization, regional differences were not expected and blocking by region was done more for drug distribution reasons. While the analysis specified in the protocol stipulated that the regional blocking factor was not to be used in the analysis models, following feedback from regulatory agencies, the models will include terms for each of the factors used in the randomization process:

- Biopsy Class (Class V versus Others)
- MMF use at screening (Yes versus No)
- Region (North America, Latin America, Europe+South Africa and Asia Pacific)

During the regulatory agency review and feedback process it was decided to remove the 'Duration of UPCR ≥0.5' endpoint from the list of key-secondary endpoints and place it within the list of 'Other Secondary Endpoints'. The proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each timepoint was also removed from the list of key secondary endpoints. To this end, neither endpoint will form part of the hierarchical testing procedure.

10 REFERENCES

1. SAS Institute Inc. The SAS System, Version 9.3. Cary, NC, SAS Institute Inc. 2012.
2. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988; 75 (4):800-2.
3. Cao, D and He, X (2011). Statistical Analysis of Adverse Events in Randomized Clinical Trials Using SAS. PharmaSUG2011 Paper SP07.

11 LIST OF TABLES, FIGURES AND LISTINGS