Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Brad H Rovin, Y K Onno Teng, Ellen M Ginzler, Cristina Arriens, Dawn J Caster, Juanita Romero-Diaz, Keisha Gibson, Joshua Kaplan, Laura Lisk, Sandra Navarra, Samir V Parikh, Simrat Randhawa, Neil Solomons, Robert B Huizinga

Lancet 2021; 397: 2070–80

Published Online May 7, 2021 https://doi.org/10.1016/S0140-6736(21)00578-X

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 27, 2021

See Comment page 2027

Department of Nephrology, The Ohio State University Wexner Medical Center, Columbus, OH, USA (Prof B H Rovin MD, S V Parikh MD); Department of Nephrology, Leiden University Medical Centre, Leiden, The Netherlands (Y K O Teng MD); Department of Medicine, SUNY Downstate Health Sciences University, Brooklyn, NY, USA (E M Ginzler MD); Department of Arthritis & Clinical Immunology, Rheumatology, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA (C Arriens MD); Department of Medicine, Division of Nephrology and Hypertension, University of Louisville School of Medicine, Louisville, KY, USA (D J Caster MD); Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico (J Romero-Diaz MD); Department of Medicine, UNC Kidney Center, Chapel Hill, NC, United States (K Gibson MD); Department of Medicine, Rutgers University, Newark, NJ, USA (J Kaplan MD); Clinical Development (L Lisk BSc, S Randhawa MD, N Solomons MD), and Research (R B Huizinga PhD), Aurinia Pharmaceuticals, Victoria, BC, Canada; University of Santo Tomas, Manila and St Luke's Medical Center, Quezon City, Philippines (S Navarra MD)

Summary

Background Voclosporin, a novel calcineurin inhibitor approved for the treatment of adults with lupus nephritis, improved complete renal response rates in patients with lupus nephritis in a phase 2 trial. This study aimed to evaluate the efficacy and safety of voclosporin for the treatment of lupus nephritis.

Methods This multicentre, double-blind, randomised phase 3 trial was done in 142 hospitals and clinics across 27 countries. Patients with a diagnosis of systemic lupus erythematosus with lupus nephritis according to the American College of Rheumatology criteria, and a kidney biopsy within 2 years that showed class III, IV, or V (alone or in combination with class III or IV) were eligible. Patients were randomly assigned (1:1) to oral voclosporin (23·7 mg twice daily) or placebo, on a background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids, by use of an interactive web response system. The primary endpoint was complete renal response at 52 weeks defined as a composite of urine protein creatinine ratio of 0·5 mg/mg or less, stable renal function (defined as estimated glomerular filtration rate [eGFR] ≥60 mL/min/1·73 m² or no confirmed decrease from baseline in eGFR of >20%), no administration of rescue medication, and no more than 10 mg prednisone equivalent per day for 3 or more consecutive days or for 7 or more days during weeks 44 through 52, just before the primary endpoint assessment. Safety was also assessed. Efficacy analysis was by intention-to-treat and safety analysis by randomised patients receiving at least one dose of study treatment. The trial is registered with ClinicalTrials.gov, NCT03021499.

Findings Between April 13, 2017, and Oct 10, 2019, 179 patients were assigned to the voclosporin group and 178 to the placebo group. The primary endpoint of complete renal response at week 52 was achieved in significantly more patients in the voclosporin group than in the placebo group (73 [41%] of 179 patients *vs* 40 [23%] of 178 patients; odds ratio 2·65; 95% CI 1·64–4·27; p<0·0001). The adverse event profile was balanced between the two groups; serious adverse events occurred in 37 (21%) of 178 in the voclosporin group and 38 (21%) of 178 patients in the placebo group. The most frequent serious adverse event involving infection was pneumonia, occurring in 7 (4%) patients in the voclosporin group and in 8 (4%) patients in the placebo group. A total of six patients died during the study or study follow-up period (one [<1%] patient in the voclosporin group and five [3%] patients in the placebo group). None of the events leading to death were considered by the investigators to be related to the study treatments.

Interpretation Voclosporin in combination with MMF and low-dose steroids led to a clinically and statistically superior complete renal response rate versus MMF and low-dose steroids alone, with a comparable safety profile. This finding is an important advancement in the treatment of patients with active lupus nephritis.

Funding Aurinia Pharmaceuticals.

Introduction

Lupus nephritis is a severe manifestation of systemic lupus erythematosus that presents with proteinuria, haematuria, and impaired kidney function. Lupus nephritis can lead to end-stage kidney disease within 10 years of diagnosis in nearly 20% of patients.[1] The ultimate goals of lupus nephritis treatment are preserving kidney function and reducing mortality, while minimising treatment-related adverse events and improving quality of life.[2,3]

A substantial and increasing body of evidence shows that an early reduction in proteinuria, particularly within 6–12 months from the start of treatment, is the single best predictor of improved long-term outcomes, including reduced risk of disease flares, end-stage kidney disease, and death.[4–8] Due to the positive predictive value of proteinuria reduction in lupus nephritis, rather than other clinical or serological markers, it has become an established, objective, and reproducible endpoint for evaluating therapeutic interventions.[2,3] Consequently, lupus nephritis treatment guidelines recommend evidence of at least 25% proteinuria reduction within 3 months and at least 50% reduction by 6 months after

Research in context

Evidence before this study

Voclosporin is a novel calcineurin inhibitor (CNI) developed for the treatment of lupus nephritis. We searched PubMed for all types of papers up to Jan 15, 2021, with search terms of ("voclosporin OR tacrolimus" [All Fields]) AND ("lupus nephritis" [All Fields]) AND ("randomized clinical trial" [All Fields]) AND ("induction" [All Fields]), which yielded publications on seven randomised trials, five of which were done in China. Two trials compared tacrolimus directly with cyclophosphamide on a background of steroids and found no difference in 6-month response rates. One trial of tacrolimus compared with mycophenolate mofetil found similar 6-month response rates and another, more recent trial showed that tacrolimus is non-inferior to mycophenolate mofetil for induction therapy. Two trials compared tacrolimus plus mycophenolate mofetil with cyclophosphamide on a background of steroids and showed a significant increase in the response rate in patients treated with tacrolimus and mycophenolate mofetil. The final study was an international, phase 2b, randomised, blinded, placebo-controlled trial that compared two different doses of voclosporin with placebo on a background of mycophenolate mofetil and steroids. There was a significant increase in 6-month complete renal response rates for the voclosporin group dosed 23·7 mg twice daily compared with placebo. The 23·7 mg twice daily dose of voclosporin was studied in this phase 3 clinical trial.

Added value of this study

This was a phase 3, randomised, placebo-controlled study assessing the efficacy and safety of voclosporin in patients with lupus nephritis. All primary and hierarchical secondary endpoints were met with use of voclosporin in combination with mycophenolate mofetil and rapidly tapered low-dose steroids. The primary endpoint was complete renal response at 52 weeks, which was longer than previous trials of CNIs in lupus nephritis. The improved efficacy shown in the voclosporin group was achieved with a steroid regimen resulting in significantly lower cumulative steroid dose than in any previous study. Results from this phase 3 trial confirm the efficacy of voclosporin shown in the phase 2 trial with an improved safety profile.

Implications of all the available evidence

Most standard therapies of lupus nephritis show a disappointing complete renal response rate and are associated with considerable toxicity, much of which is due to the use of high-dose steroids during the initial phase of treatment. The totality of the data suggest that the addition of a CNI such as voclosporin to background immunosuppressive therapy as a first-line treatment will significantly increase the proportion of patients with lupus nephritis achieving compete renal response at 6 and 12 months compared with background therapy alone. The improved complete renal response rate in this study is realised with far less corticosteroid than traditionally used in the treatment of lupus nephritis, and a moderate dose of mycophenolate mofetil.

Correspondence to:
Dr Robert Huizinga, Research, Aurinia Pharmaceuticals, Victoria, BC V8Z 7X8, Canada
rhuizinga@auriniapharma.com

initiating treatment, with a target proteinuria ratio of <0·5–0·7 mg/mg within the first year of treatment.[3] However, up to 60% of patients are unable to achieve these treatment targets with current therapeutic options, most of which are used off label.[5,9] There is a clear need for more effective treatments eliciting an early treatment response and ideally allowing for a reduction in steroid use.[2,10–12]

The addition of calcineurin inhibitors (CNIs) to an immunosuppressive regimen in studies of predominantly Asian patients with lupus nephritis has been shown to improve renal response rates with a lower dose of steroids and mycophenolate mofetil (MMF) than used conventionally.[13–15] The general applicability of these data was not clear because the CNI regimen had not been tested in ethnically and racially diverse patients with lupus nephritis.

Voclosporin, a novel CNI developed for the treatment of lupus nephritis, has several advantages compared with traditional CNIs. These include a consistent pharmacokinetic profile eliminating the need for therapeutic drug monitoring required for other CNIs and a more favourable effect on lipids and glucose concentrations compared with other CNIs.[16,17] Additionally, voclosporin has no effect on concentrations of mycophenolic acid, the active moiety of MMF.[18] Voclosporin doses of 23·7 mg twice daily and 39·5 mg twice daily were compared with placebo in a phase 2 randomised controlled trial of patients with lupus nephritis (NCT02141672; AURA-LV); the 23·7 mg dose in combination with MMF and rapidly tapered low-dose oral steroids resulted in significantly higher complete renal response rates at 24 and 48 weeks of treatment and was chosen for further evaluation.[19] Here we present the results of the AURORA 1 phase 3 international, randomised controlled trial, which aimed to determine the efficacy and safety of voclosporin versus placebo added to MMF and low-dose oral steroids for the treatment of patients with active lupus nephritis in an ethnically and racially diverse patient population.

Methods

Study design and participants

This phase 3, multicentre, double-blind, randomised trial was done in 142 hospitals and clinics across 27 countries in North and Latin America, Europe, South

Africa, and Asia. Treatment allocation remains masked for patients that subsequently enrolled into the ongoing phase 3 extension study (NCT03597464; AURORA 2).

Eligible patients had a diagnosis of systemic lupus erythematosus with lupus nephritis according to the American College of Rheumatology criteria, and a kidney biopsy within 2 years of screening that showed class III, IV, V (alone or in combination with class III or IV) lupus nephritis. Lupus nephritis had to be active as defined by patients having a current urine protein creatinine ratio (UPCR) of 1·5 mg/mg or more (or ≥2 mg/mg if pure class V) by first morning void urine. Patients who had a kidney biopsy more than 6 months before screening were required to have a doubling or greater increase in UPCR in the 6 months before screening. Patients were ineligible if their estimated glomerular filtration rate (eGFR) was 45 mL/min per 1·73 m² or less at screening. The full list of inclusion and exclusion criteria is shown in the appendix (pp 6, 7).

A masked, independent Clinical Endpoints Committee (CEC) adjudicated primary and select secondary endpoints before database lock. An independent Data and Safety Monitoring Board monitored the safety of study participants and efficacy of treatment. An Institutional Review Board or Independent Ethics Committee at each participating site approved the informed consent form and protocol. All patients provided written informed consent, the content of which was in accordance with the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines.

Randomisation and masking

An interactive web response system was used to randomly assign patients (1:1) to voclosporin or matched placebo. The randomisation schema (stratification) was generated by a masked statistician not involved in the study. The randomisation was stratified by biopsy class (pure class V only *vs* others), previous MMF use at the time of screening (yes *vs* no), and region (North America *vs* Latin America *vs* Europe and South Africa *vs* Asia-Pacific). Randomisation was accessed by the investigator at the baseline visit using the interactive web response system. Patients, investigators, and the sponsor remained masked to the randomisation assignment for the duration of the study.

Procedures

Patients received oral 23·7 mg voclosporin (given as three 7·9 mg softgel capsules; voclosporin group) or matching placebo twice daily for 52 weeks (appendix p 10). The dosing schedule in the placebo group was the same as that of the active treatment group. Voclosporin and placebo were identical in taste, smell, and appearance. All patients were administered intravenous methylprednisolone once daily on days 1 and 2 (0·5 g/day for patients that weighed more than 45 kg and 0·25 g/day for patients that weighed less than 45 kg). All patients then began a rapid taper of oral prednisone on day 3 commencing at 20–25 mg per day. The dose decreased over time to 2·5 mg per day at week 16 according to a protocol predefined schedule and, thereafter, adjusted at investigator discretion (appendix p 10). MMF was administered at a dose of 1 g twice daily for a total daily dose of 2 g. Patients who were not already taking MMF before randomisation received 1 g per day for the first week, increasing to 2 g per day from day 8. Patients receiving MMF before randomisation continued their dose without interruption. Doses of MMF up to 3 g per day were permitted with approval of the medical monitor. Patients receiving angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers for the treatment of hypertension must have been on a stable dose for at least 4 weeks before randomisation and continued that same dose throughout the trial.

See Online for appendix

Because of the expected haemodynamic effects of CNIs,[17] the protocol provided specific guidance to interrupt study treatment for any patient experiencing a more than 30% decrease in eGFR (calculated with the Chronic Kidney Disease Epidemiology Collaboration equation) from baseline to less than 60 mL/min per 1·73 m² or to reduce treatment for a more than 20% but less than 30% decrease in eGFR from baseline. Upon a repeat test confirming a return to within acceptable limits, study treatment could then be restarted at a lower dose and increased as tolerated based on renal function (appendix p 11). For all patients, target systolic blood pressure was 130 mm Hg or lower and target diastolic blood pressure was 80 mm Hg or lower. Study treatment was to be withheld in case of systolic blood pressure higher than 165 mm Hg or diastolic blood pressure higher than 105 mm Hg and symptoms of hypertension; restarting study treatment required discussion with the medical monitor.

UPCR was assessed with first morning void urine at all study visits (weeks 1, 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 52). Additionally, 24 h urinalysis samples to measure UPCR were collected at weeks 24 and 52. Anti-double-stranded DNA was assessed by automated fluorescence immunoassay at screening, week 24, and week 52. Safety and adverse events were assessed through laboratory assessments, vital signs, and physical examinations. Adverse events were defined as an adverse event occurring on or after the first dose of voclosporin or placebo up to and including 30 days after the last dose. Adverse events were aggregated by System Organ Class and Preferred Term and coded using Medical Dictionary for Regulatory Activities version 20.0.

Outcomes

The primary endpoint was complete renal response at week 52 assessed by the CEC and defined as a composite of UPCR of 0·5 mg/mg or less, eGFR of 60 mL per min

or more or no confirmed eGFR decrease of more than 20% from baseline, no administration of rescue medication, and no more than 10 mg prednisone equivalent per day for 3 or more consecutive days or for 7 or more days in total during weeks 44 through 52, just before the primary endpoint assessment.

Key secondary hierarchical endpoints were (in order) time to UPCR of 0·5 mg/mg or less, partial renal response (defined as ≥50% reduction from baseline UPCR) at weeks 24 and 52, time to 50% reduction in UPCR from baseline, and complete renal response at week 24 (based on primary endpoint definition with steroid dosing assessed from weeks 16 to 24). Additional secondary endpoints (not part of the hierarchical order) were the proportion of patients experiencing a confirmed decrease from baseline in eGFR (prespecified as a >30% decrease); duration of UPCR of 0·5 mg/mg or less (defined as the time [days] from the onset of the first UPCR ≤0·5 mg/mg to the subsequent, second occurrence of UPCR >0·5 mg/mg); change in UPCR, serum creatinine, urine protein, and eGFR from baseline at each timepoint; change from baseline in immunology parameters (complement 3, complement 4, and anti-double-stranded DNA) at weeks 24 and 52; change from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) scores.

Complete definitions of the primary and secondary endpoints are provided in the appendix (p 8).

Statistical analysis

This study was designed to have 80% power with a 0·05 two-sided significance level to detect the difference between a complete renal response rate of 20·0% in the placebo group and of 34·4% in the voclosporin group (odds ratio [OR] of 2·1, as determined by a two-group continuity corrected χ^2 test, indicative of a clinically relevant effect) with a planned sample size of 162 patients in each group.

The primary and hierarchical secondary efficacy analyses were done in the intention-to-treat population and done using a logistic regression model. Safety analyses included all patients who received at least one dose of study treatment. Hierarchical key secondary endpoints were analysed using the Hochberg step-up sequential testing procedure. Patients withdrawing for any reason were counted as non-responders in the primary analysis; therefore, no adjustment of sample size for withdrawals was necessary.

Prespecified covariate analyses were done using a logistic regression model to evaluate the primary endpoint in the following subgroups: age (≤30 years *vs* >30 years), sex, race (White *vs* Asian *vs* other), region (Asia-Pacific *vs* Europe and South Africa *vs* Latin America *vs* North America), biopsy class (class V *vs* other), use of MMF at screening (yes *vs* no), and maximum daily dose of MMF during the study period (≤2 g *vs* >2 g). A post-hoc analysis evaluated additional race (White *vs* Asian *vs* Black *vs* other) and ethnicity (Hispanic or Latino *vs* non-Hispanic or non-Latino) subgroups. The study was not powered to detect a statistically significant difference between subgroups.

Secondary time to event endpoints were estimated by the Kaplan-Meier methods. Cox's proportional hazards model assessed the significance of the differences between treatment groups.

Change from baseline secondary endpoints were analysed using a Mixed Effect Model Repeated Measures (MMRM) analysis. To account for baseline hyperfiltration, summary tables and endpoint analyses

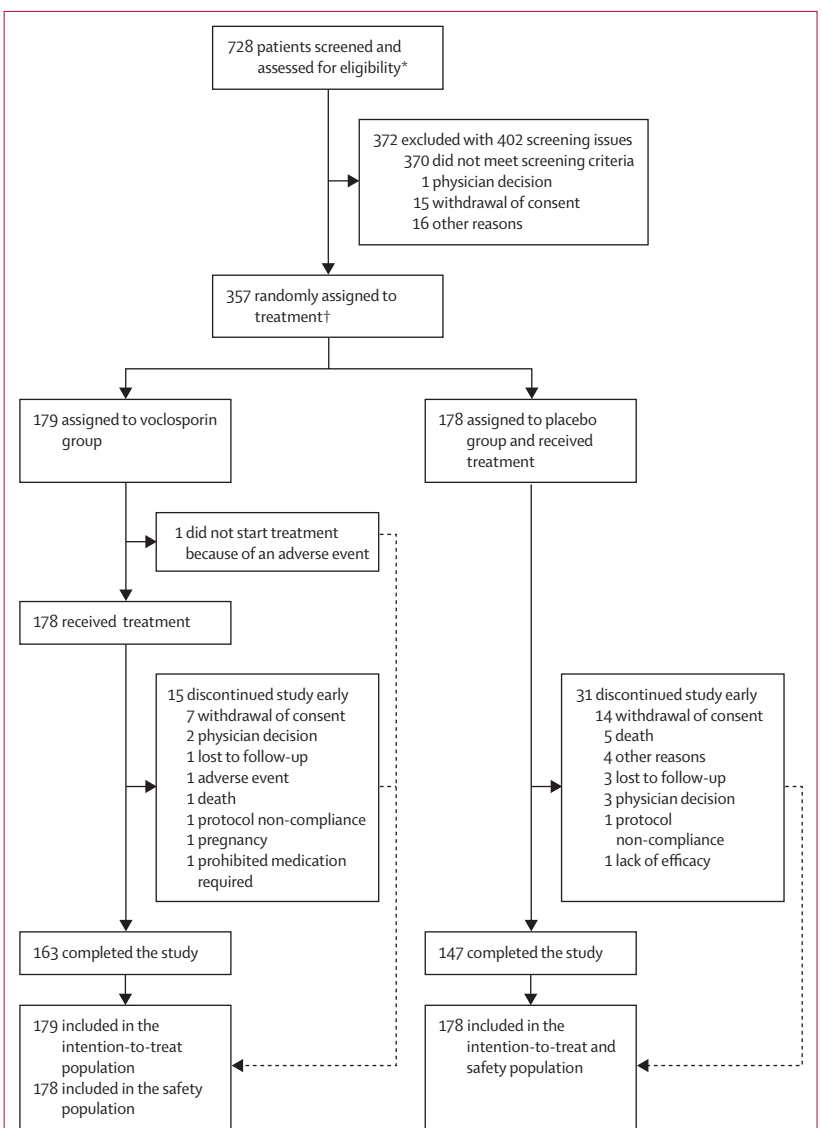

Figure 1: **Trial profile**
*30 patients had two screening visits. †One patient was randomised in error; they were recorded in the database as not being eligible after screening and also as a randomised patient (their data were included in the intention-to-treat population).

	Voclosporin group (n=179)	Placebo group (n=178)
Median age, years	31 (18–62)	32 (18–72)
Sex		
Male	18 (10%)	26 (15%)
Female	161 (90%)	152 (85%)
Mean weight, kg	66·49 (17·07)	66·55 (16·11)
Race*		
White	68 (38%)	61 (34%)
Black	26 (15%)	19 (11%)
Asian	53 (30%)	56 (31%)
Other†	32 (18%)	42 (24%)
Ethnicity*		
Hispanic or Latino	57 (32%)	59 (33%)
Non-Hispanic or non-Latino	122 (68%)	118 (66%)
Unknown	0	1 (1%)
Region		
North and Latin America	75 (42%)	74 (42%)
Europe and South Africa	52 (29%)	52 (29%)
Asia-Pacific	52 (29%)	52 (29%)
Mean time since initial lupus nephritis diagnosis, years	4·6 (5·1)	4·7 (4·9)
Mean time since systemic lupus erythematosus diagnosis, years	6·6 (6·4)	6·9 (6·1)‡
Biopsy class		
Pure class III	20 (11%)	29 (16%)
Pure class IV	91 (51%)	77 (43%)
Pure class V	25 (14%)	25 (14%)
Class II and V only	0	1 (<1%)
Class III and V only	24 (13%)	20 (11%)
Class IV and V only	19 (11%)	26 (15%)
Baseline eGFR		
Mean, mL/min per 1·73 m²	92·1 (30·6)	90·4 (29·0)
High (≥60 mL/min per 1·73 m²)	146 (82%)	144 (81%)
Mean baseline UPCR, mg/mg	4·14 (2·71)	3·87 (2·36)
Complement 3		
Mean, mg/dL	81·6 (34·73)	86·9 (36·42)
Low (<90 mg/dL)	105 (59%)	99 (55%)
Complement 4		
Mean, mg/dL	16·6 (11·5)	16·8 (9·7)
Low (<10 mg/dL)	50 (28%)	45 (25%)
Anti-double-stranded DNA		
Mean, IU/mL	105·2 (127·7)	94·7 (124·4)
High (>10 IU/mL)	133 (74%)	118 (66%)
SELENA-SLEDAI		
n	177	177
Mean	13·2 (6·5)	11·8 (6·1)
MMF use at screening		
Yes	100 (56%)	96 (54%)
No	79 (44%)	82 (46%)

Data are median (range), n (%), or mean (SD), unless stated otherwise. Percentages might not add up to 100% because of rounding. eGFR=estimated glomerular filtration rate. UPCR=urine protein creatinine ratio. SELENA-SLEDAI=Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index. MMF=mycophenolate mofetil. *Analyses for race and ethnicity were post hoc. †Other races include American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and other or mixed races except mixed Black race. ‡Data missing for one patient.

Table 1: **Demographic and baseline patient characteristics in the intention-to-treat population**

incorporating eGFR used a corrected eGFR with a prespecified ceiling of 90 mL/min per 1·73 m², with all eGFR values higher 90 mL/min per 1·73 m² constrained to 90 mL/min per 1·73 m². eGFR change from baseline analyses were also calculated using non-corrected eGFR values.

Mean changes from baseline were analysed using a restricted maximum likelihood-based repeated measures approach in combination with the Newton Raphson Algorithm. Analyses included the fixed, categorical effects of treatment, investigative site, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline scores of laboratory parameters. A common unstructured covariance structure was used to model the within-patient errors, or an autoregressive covariance matrix in the absence of convergence. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Significance tests were based on least-squares means using a two-sided α of 0·05 (two-sided 95% CIs).

All statistical analyses were done with SAS PROC MIXED (version 9.3).

This trial is registered with ClinicalTrials.gov, NCT03021499, and EudraCT, 2016–004045–81.

Role of the funding source

The study was sponsored by Aurinia Pharmaceuticals (Aurinia) and the sponsor was responsible for the overall conduct of the study. Aurinia was involved in data collection, data analysis, data interpretation, and provided funding for medical writing support. Aurinia reviewed the final manuscript before submission, but the authors retained editorial control.

Results

Between April 13, 2017, and Oct 10, 2019, 357 patients were enrolled in the trial, of whom 179 patients were randomly assigned to the voclosporin group (intention-to-treat population) and 178 patients to the placebo group (intention-to-treat population). One patient in the voclosporin group did not start treatment because of an adverse event. 163 (91%) of 179 patients in the voclosporin group and 147 (83%) of 178 in the placebo group completed

the study (figure 1). 15 (8%) of 178 patients in the voclosporin group and 31 (17%) of 178 patients in the placebo group discontinued the study; discontinuation reasons were similar in both groups (figure 1). The majority of patients (318 [89%] of 357) had a kidney biopsy within the 6 months before screening; 39 (11%) had a biopsy more than 6 months before screening, including 12 (3%) patients who had a biopsy more than 12 months before screening. Baseline characteristics were balanced between the two groups (table 1).

The overall duration of exposure and daily exposure to voclosporin or placebo were similar for both treatment groups; the median compliance as assessed by returned medication container capsule count was approximately 99% in both groups. Oral steroid doses were tapered per protocol guidance; at week 16, 142 (82%) of 174 patients in the voclosporin group and 138 (81%) of 171 patients in the placebo group were on an oral steroid dose of 2·5 mg or less, whereas these patients proportions decreased to 121 (75%) of 162 patients in the voclosporin group and 108 (73%) of 147 patients in the placebo group at week 52. Exposure to MMF was similar for treatment groups in terms of duration of exposure and mean daily dose, which was 2 g per day (SD 0·4) in both groups. A total of 44 patients received at least one dose of MMF of more than 2 g per day (16 [9%] patients in the voclosporin group and 28 [16%] patients in the placebo group); eight patients in each group were on 3 g per day MMF at the beginning of the study, of whom four (2%) patients in the voclosporin group and six (3%) patients in the placebo group continued the dose throughout the study.

In the analysis of the primary endpoint, significantly more patients in the voclosporin group than in the placebo group had a complete renal response (73 [41%] of 179 patients *vs* 40 [23%] of 178 patients; OR 2·65; 95% CI 1·64–4·27; p<0·0001; table 2). The absolute difference between groups for achieving a complete renal response was 18% in favour of voclosporin. All of the composite measures of the primary endpoint of complete renal response occurred more often in patients in the voclosporin group, but this difference was statistically significant only for UPCR of 0·5 mg/mg or less (appendix p 11).

All hierarchical key secondary endpoints achieved statistical significance in favour of voclosporin. The proportion of patients achieving a complete renal response at week 24 was significantly higher in the voclosporin group than the placebo group (table 2). More patients in the voclosporin group achieved a partial renal response at weeks 24 and 52 than in the placebo group (table 2; figure 2). As shown in the Kaplan-Meier plots, the time-to-event curves begin to separate within the first month of treatment, showing an early treatment response in the voclosporin group; the difference between the two treatment groups was sustained throughout the study (figure 3). More patients in the voclosporin group than in the placebo group achieved an UPCR of 0·5 mg/mg or less during the study (116 [65%] of 179 patients *vs* 78 [44%] of 178 patients) and the time to reach this threshold was significantly shorter for the voclosporin group (figure 3). A 50% reduction in UPCR from baseline at any time during the study was achieved by 173 (97%) patients treated with voclosporin compared with 135 (76%) patients receiving placebo. The median time to achieve a 50% reduction in UPCR was significantly shorter for the voclosporin group than in the placebo group (figure 3). In an analysis of duration of UPCR of 0·5 mg/mg or less, the median time was 198 days (95% CI 103–non-calculable) in the placebo group and 216 days (127–non-calculable) in the voclosporin group; results were not significant (p=0·65). In an analysis of mean UPCR over time, there was a

	Voclosporin group (n=179)	Placebo group (n=178)	OR or HR (95% CI)	p value
Primary endpoint*				
Complete renal response at 52 weeks	73 (41%)	40 (23%)	OR 2·65 (1·64–4·27)	<0·0001
Secondary endpoints				
Complete renal response at 24 weeks	58 (32%)	35 (20%)	OR 2·23 (1·34–3·72)	0·002
Partial renal response at 24 weeks	126 (70%)	89 (50%)	OR 2·43 (1·56–3·79)	<0·001
Partial renal response at 52 weeks	125 (70%)	92 (52%)	OR 2·26 (1·45–3·51)	<0·001
Time to UPCR ≤0·5 mg/mg, days	169 (141–214)	372 (295–NC)	HR 2·02 (1·51–2·70)	<0·001
Time to 50% reduction in UPCR, days	29 (29–32)	63 (57–87)	HR 2·05 (1·62–2·60)	<0·001

Data are n (%) or median (95% CI), unless otherwise specified. OR=odds ratio. HR=hazard ratio. UPCR=urine protein creatinine ratio. NC=non-calculable. *The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, mycophenolate mofetil use at baseline, and region.

Table 2: **Summary of complete and partial renal responses at weeks 24 and 52 (intention-to-treat population)**

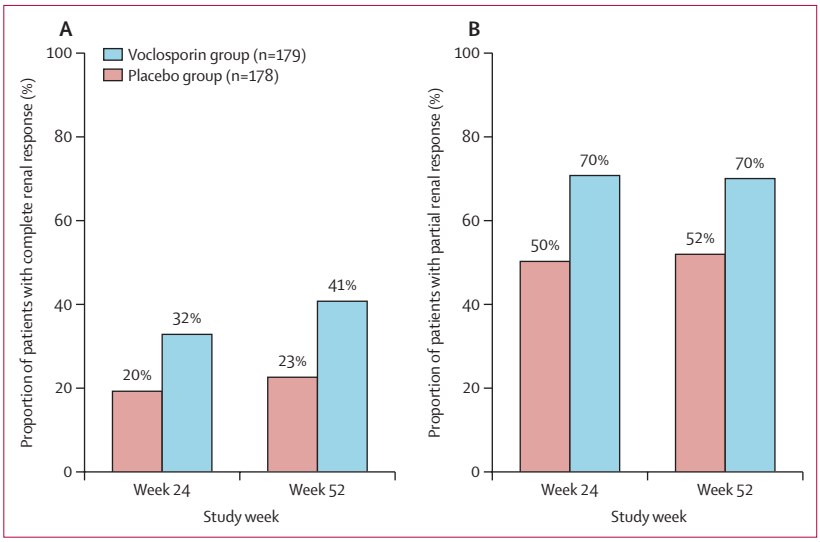

Figure 2: **Complete and partial renal response endpoints (intention-to-treat population)**

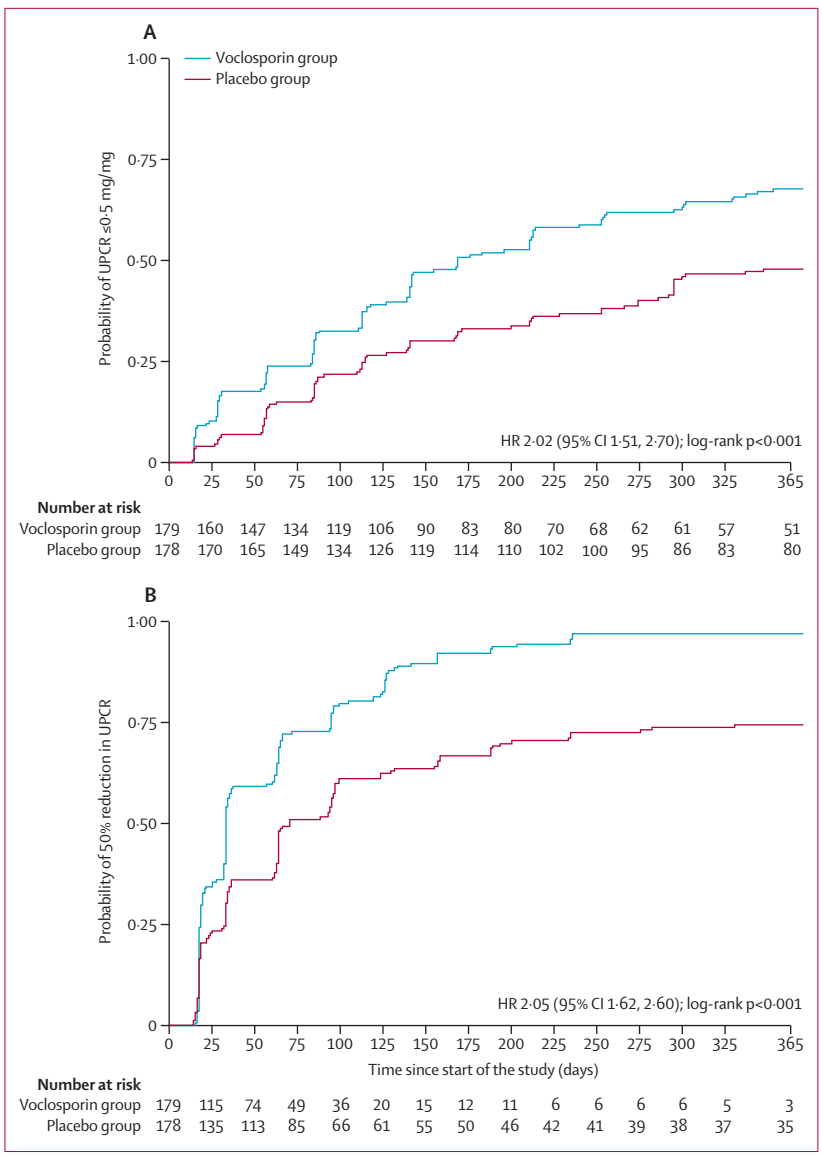

***Figure 3*: Probability of UPCR of ≤0·5 mg/mg (A) and of ≥50% reduction from baseline in UPCR (B; intention-to-treat population)**

Percentiles are Kaplan-Meier estimates. The HRs are from a Cox's proportional hazards model with covariates for treatment group, baseline UPCR, biopsy class, mycophenolate mofetil use at baseline, and region. HR=hazard ratio. UPCR=urine protein creatinine ratio.

significantly greater decrease at week 52 from baseline for patients in the voclosporin group (decrease of 2·65 mg/mg from baseline to 1·35 mg/mg at week 52) than for patients in the placebo group (decrease of 1·88 mg/mg from baseline to 1·94 mg/mg at week 52; 95% CI –1·52 to –0·46; p<0·001).

There was a decrease in mean SELENA-SLEDAI index scores at weeks 24 and 52, with no statistically significant differences between groups (p=0·38 at week 24 and p=0·28 at week 52; appendix p 12). Changes from baseline in immunology serology parameters (complement 3, complement 4, and anti-double-stranded DNA) were similar in both groups, with the MMRM analyses showing improvements at week 52 for all parameters without statistically significant difference between treatment groups (appendix p 14).

Subgroup analyses of the primary endpoint at week 52 resulted in OR higher than 1 indicating a higher complete renal response rate in the voclosporin treatment group than in the placebo group in all subgroups (figure 4). Results were significant as shown with 95% CIs that did not cross 1 for all sex; age; ethnicity subgroups; Asian, Black, and other race; Asia-Pacific and Latin America region; other biopsy class; and MMF used at screening and maximum MMF dose during the study of 2 g/day or less. Results were not significant for the White race; pure class V; Europe and South Africa or North America region; and no MMF used at screening and maximum MMF dose during the study of more than 2 g/day subgroups.

The adverse event profile was balanced between the two groups (table 3). Infections and infestations were the most common type of adverse events in both groups with the majority of events being mild or moderate in intensity. Serious adverse events occurred in 37 (21%) of 178 in the voclosporin group and 38 (21%) of 178 patients in the placebo group. The most frequent serious adverse event involving infection was pneumonia, occurring in 7 (4%) patients in the voclosporin group and in 8 (4%) patients in the placebo group. A total of six patients died during the study or study follow-up period (one [<1%] patient in the voclosporin group and five [3%] patients in the placebo group). Three (2%) patients in the placebo group died as a result of adverse events occurring during the study treatment period (pneumonia, pneumonia and septic shock, and lupus nephritis). In addition, two patients in the placebo group and one patient in the voclosporin group died due to adverse events that started more than 30 days after discontinuation of study drug (placebo group: pulmonary embolism and acute respiratory failure; voclosporin group: nosocomial pneumonia). None of the events leading to death were considered by the investigators to be related to the study treatments.

Mean lipid concentrations (cholesterol, low-density lipoprotein cholesterol, and triglycerides) were higher than normal at baseline and decreased in both treatment groups during the study with significantly greater decreases occurring in the voclosporin group for cholesterol and low-density lipoprotein cholesterol at week 52 (appendix p 13). Mean haemoglobin A1c and serum glucose concentrations remained stable in both groups throughout the study (appendix p 15). The incidence of new onset diabetes was reported for only one patient in the study; this patient was in the placebo group. Mean concentrations of magnesium and potassium remained within the normal range for both treatment groups (appendix p 16).

At baseline, mean corrected eGFR measurements were similar in both groups. There was a slight early

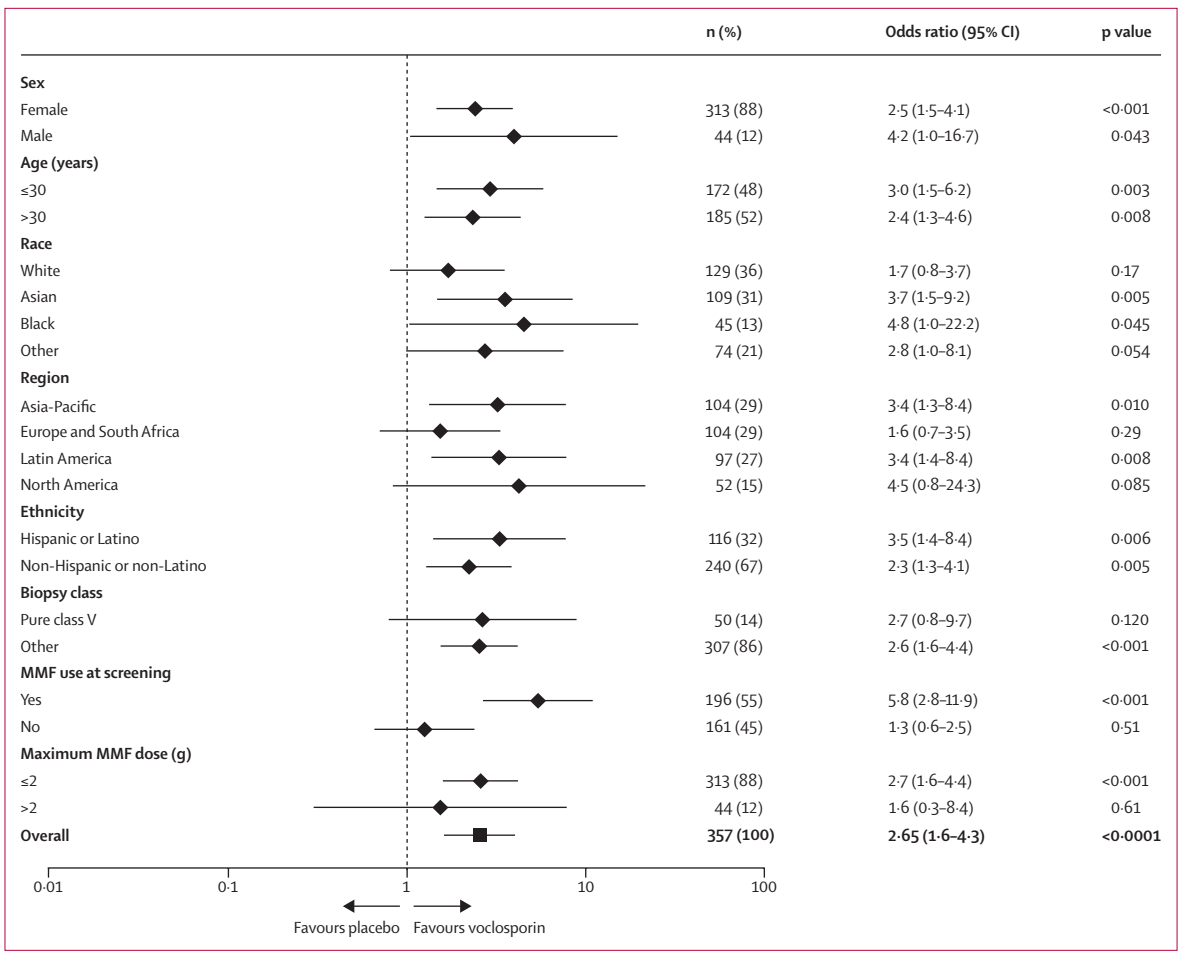

Figure 4: **Subgroup analysis of primary outcome of complete renal response at week 52 (intention-to-treat population)**
Analysis uses a logistic regression model with covariates for study, treatment group, subgroup, and treatment by subgroup interaction. Race and ethnicity analyses were post hoc. MMF use at screening was determined by nominal yes or no question at screening visit. Maximum MMF dose reflects the maximum daily dose of MMF received during the study. MMF=mycophenolate mofetil.

eGFR decrease of 1·5 mL/min per 1·73 m² at week 2 in the voclosporin group that returned to near baseline levels by week 4 and remained stable for the duration of the study (appendix p 17). A least square mean analysis of corrected eGFR from weeks 4 to 52 showed a positive slope of 1·1 for placebo and 1·0 for voclosporin. The mean corrected eGFR change from baseline was less than 5 mL/min per 1·73 m² for both treatment groups at all study treatment timepoints. 18 (10%) patients in each group had a confirmed prespecified eGFR decrease (prespecified as a >30% decrease from baseline) at any time throughout the study; few patients discontinued study drug due to eGFR decrease (3 [2%] of 178 in the voclosporin group and 4 [2%] of 178 patients in the placebo group) indicating eGFR decreases were largely reversible. Investigator reported incidence of serious renal dysfunction was 3% in the voclosporin group and 2% in the placebo group. Mean serum creatinine concentrations remained within the normal range in both groups (appendix p 17). There was a small increase in mean systolic blood pressure in the voclosporin group at week 2 of 3·9 mm Hg which returned to baseline by week 8; overall there was an improvement in mean blood pressure over the study period with no statistically significant difference between groups (appendix p 18).

Discussion

In this phase 3 trial, the primary endpoint was met with patients receiving voclosporin in combination with background MMF and low-dose steroids achieving a clinically meaningful and significantly higher complete renal response rate at 1 year compared with patients receiving MMF and low-dose steroids alone. All prespecified hierarchical secondary endpoints were significantly in favour of voclosporin, including partial renal response at weeks 24 and 52, time to UPCR of 0·5 mg/mg or less, and time to 50% reduction in UPCR, reinforcing the successful primary endpoint result. Notably, a significant reduction in proteinuria (as

	Voclosporin group (n=178)	Placebo group (n=178)
Adverse event summary		
Adverse event	162 (91%)	158 (89%)
Serious adverse event	37 (21%)	38 (21%)
Serious adverse event of infections and infestations	18 (10%)	20 (11%)
Treatment-related serious adverse event	8 (4%)	8 (4%)
Adverse event leading to study drug discontinuation	20 (11%)	26 (15%)
Death*	1 (<1%)	5 (3%)
Treatment-related adverse event leading to death	0	0
Adverse events (reported ≥4% of patients)		
Infections and infestations	115 (65%)	101 (57%)
Gastrointestinal disorders	83 (47%)	61 (34%)
Investigations and infestations	60 (34%)	31 (17%)
Nervous system disorders	47 (26%)	27 (15%)
Skin and subcutaneous tissue disorders	42 (24%)	31 (17%)
Musculoskeletal and connective tissue disorders	40 (22%)	46 (26%)
Vascular disorders	38 (21%)	23 (13%)
General disorders and administration site conditions	36 (20%)	32 (18%)
Blood and lymphatic system disorders	35 (20%)	29 (16%)
Respiratory, thoracic, and mediastinal disorders	26 (15%)	17 (10%)
Renal and urinary disorders	26 (15%)	37 (21%)
Metabolism and nutritional disorders	25 (14%)	37 (21%)

Adverse events are defined as an adverse event that occurs on or after the day of the first dose and up to 30 days after the last dose of voclosporin or placebo, with the exception of death. *Includes two deaths in placebo group and one death in voclosporin group that occurred >30 days after discontinuation of study drug.

Table 3: **Adverse events (safety population)**

measured by UPCR) in the voclosporin group was achieved within the first 6 months of the study and maintained at 52 weeks; the median time to 50% reduction in UPCR in the voclosporin group of 29 days was significantly shorter than the 63 days in the control group. These results are encouraging as the rapid reduction of proteinuria within the first year of treatment is a crucial outcome associated with preservation of kidney function and improvement of long-term outcomes.[4–6,8]

This study showed that a rapidly tapered low-dose steroid regimen can be effective in the treatment of lupus nephritis, reducing the risk of organ damaging and toxic effects of prolonged corticosteroid use.[20,21] The steroid regimen used in both treatment groups of this study resulted in lower steroid exposure while maintaining efficacy; the control group in this study achieved complete renal response rates consistent with historical studies involving higher steroid doses.[9,10,13]

A subgroup analysis of the primary endpoint showed a consistent trend of improved complete renal response with voclosporin treatment with OR higher than 1 in all subgroups, including the small group of patients with pure class V lupus nephritis, although not all differences between groups were statistically significant. Furthermore, the study included a large and racially diverse population, with geographical representation from both North and Latin America, Europe, South Africa, and Asia-Pacific, and racial and ethnic representation including Black, Hispanic, Latino, and Asian populations, with similar response rates in all subgroups. The response to voclosporin was notable among Black patients, who are more likely to have worse outcomes to lupus nephritis therapies than patients of other races.[22,23] This study provides additional evidence on the efficacy of CNI-based regimens in diverse populations as seen in the phase 2 voclosporin study[19], and importantly extends the data from studies in predominantly Asian populations.[15,19,24–27] Interpretation of all subgroup findings should be tempered by the fact that the study was not designed to detect statistically significant differences between subgroups.

The safety profile of voclosporin was comparable with that of placebo on a background of MMF and low-dose steroids in this 52-week trial. The adverse events observed in both treatment groups were as expected for the population and treatment regimen.[10–12,19] It is reassuring that mortality was lower in the voclosporin group of this study, in contrast to the imbalance of deaths seen in the voclosporin group in the phase 2 study.[19] Additionally, infection-related adverse events were balanced across both groups. Voclosporin had a favourable effect on lipids and no significant impact on glucose, dose-related effects, which have been particularly noted for cyclosporine and tacrolimus.[28] Mean values for blood pressure and electrolytes were stable throughout the study; importantly, magnesium and potassium remained within normal limits with no observed evidence of tubular toxicity. It is encouraging that at 52 weeks of treatment in this study there was no indication of worsening renal function or progression. Renal function remained stable over time for both groups as seen by the eGFR slopes; the reduction in mean eGFR for the voclosporin group was generally mild and occurred soon after initiation of voclosporin, without further decline, consistent with the well described haemodynamic effect of CNIs.[17]

Voclosporin has a consistent pharmacokinetic and pharmacodynamic profile that eliminates the need for therapeutic drug monitoring and potentially results in improved safety compared with other CNIs.[18] Additionally, voclosporin does not affect concentration of mycophenolic acid, the active moiety of MMF, which is often used for the treatment of lupus nephritis.[16,18]

CNIs have two complementary mechanisms of action pertinent to the treatment of lupus nephritis. The well

characterised immunosuppressive mechanism involves reduction of proinflammatory cytokine transcription, resulting in decreased T-cell activation. In addition, CNIs have a protective effect on podocytes preventing degradation of the protein synaptopodin; synaptopodin is then able to maintain the integrity of the podocyte actin cytoskeleton. The action of CNIs in supporting podocyte structure and function might be disease-modifying in lupus nephritis as podocyte damage leads to increases in proteinuria and is associated with disease progression.[29–31] The rapid reduction of proteinuria, observed early in the voclosporin group in this trial and maintained at 52 weeks, is consistent with the studied effects of other CNIs, and might be of benefit for long-term preservation of kidney health.[4–7]

Recent studies in lupus nephritis, including the current study, show that after 1 year of standard-of-care treatment with routinely used therapies, approximately 20–30% of patients achieve a complete renal response. In these studies, novel therapies have thus far shown up to a 20% improvement in achieving complete renal response compared with standard-of-care.[9,32] This finding might be useful in designing future lupus nephritis trials.

A limitation of this study is that activity and chronicity indices were not assessed. Although most patients had biopsies within 6 months of screening, to assess activity and chronicity would have required all patients to have a biopsy just before enrolment. Additionally, this study did not collect information on dose of MMF before enrolment, did not differentiate response to treatment in patients with new onset compared with relapsed lupus nephritis, or evaluate extra-renal systemic lupus erythematosus activity.

Another limitation of this study is that it was only of 52 weeks duration. Lupus nephritis is chronic disease and it is important to evaluate the long-term effects of therapeutic interventions in terms of both efficacy and safety. We anticipate results from the ongoing AURORA 2 extension study, which will provide further safety and efficacy data on the combination of voclosporin with MMF and low-dose steroids with an additional 2 years of treatment.

The present study enrolled patients with a recent biopsy showing active lupus nephritis, or a biopsy from 6 months to 2 years showing lupus nephritis with current clinical evidence of renal flare, mirroring real-world clinical practice. Results showed superior efficacy of voclosporin compared with placebo in combination with MMF and low-dose steroids, confirming the early treatment response and overall treatment efficacy observed with voclosporin in the phase 2 trial.[19] Together results from the phase 2 and phase 3 voclosporin clinical studies represent an important advancement in the treatment of patients with active lupus nephritis.

Contributors

NS and RBH conceived and designed the trial and protocol. SVP was the principal investigator. SVP and YKOT contributed to the trial design and protocol. YKOT, EMG, CA, DJC, JR-D, KG, JK, and SN were study site investigators and contributed to implementation of the study and data collection. LL, SR, NS, and RBH were responsible for execution of the study. LL, NS, RBH, and SR were responsible for statistical analyses with additional oversight by Matt Truman (Truman Statistical Services, Sydney, NSW, Australia), the AURORA 1 study statistician. All authors contributed to data analysis, interpretation of study results, and preparation of the report. BHR, YKOT, EMG, and SR prepared the first draft of the manuscript. All authors had access to all of the data from the study and BHR, YKOT, EMG, LL, SR, NS, and RBH verified the raw data. All authors critically reviewed and edited the manuscript and approved the final version for submission.

Declaration of interests

BHR reports personal fees from Aurinia, Callidatis, ChemoCentryx, Retrophin, Novartis, Morphosys, EMD Serono, Bristol Myers Squibb, Janssen, Omeros, and AstraZeneca; non-financial support from Lupus Foundation of America; and grants from National Institutes of Health (NIH), outside the submitted work. YKOT reports consultancy fees from Aurinia, during the conduct of the study. EMG was a site primary investigator for clinical trials funded by Aurinia. CA reports personal fees from Aurinia, during the conduct of the study; grants and personal fees from Bristol Myers Squibb and GlaxoSmithKline; and grants from Exagen, outside the submitted work. DJC reports grants from NIH; and personal fees from Aurinia, Calliditas, GlaxoSmithKline, and Retrophin, outside the submitted work. JR-D participated in Aurinia clinical trials. KG reports grants and personal fees from Aurinia, and Retrophin; grants from Bristol Meyer Squibb; and personal fees from Reata, outside the submitted work. JK reports personal fees from and is a stakeholder of Aurinia Pharmaceuticals, outside the submitted work. SN was a consultant or participated in speaker bureau for Astellas, Pfizer, Novartis, Boehringer Ingelheim, and Johnson and Johnson; received educational and research grants from Astellas and Aurinia; and participated in Aurinia clinical trials. SVP was a consultant for Aurinia, GlaxoSmithKline, Bristol Myers Squibb; received research funding from National Institute of Diabetes and Digestive and Kidney Diseases, EMD Serono, Aurinia, and Mallinckrodt; and participated in clinical trials of Aurinia. NS is an employee and stockholder of Aurinia and has an issued patent (number 10286036, on a voclosporin dosing protocol). LL, SR, and RBH are employees and stockholders of Aurinia.

Data sharing

The data underlying this Article, the study protocol, and statistical analysis plan will be shared with researchers on reasonable request to the corresponding author. Data will be shared through a secure online platform after signing a data access agreement. Data will be available at the time of publication and for a minimum of 5 years from the end of the trial.

Acknowledgments

The study and publication were funded by Aurinia Pharmaceuticals. We thank all AURORA 1 investigators, study site coordinators, and patients who participated in this study. We also thank Matt Truman, study statistician; the following members of the Drug Safety Monitoring Board: Arif Khwaja, James Sawyer, and Ed Vital; and the following members of the Clinical Endpoints Committee: Ian Bruce, Daniel Cattran, Teun van Gelder, Colin Hayward, and Md Yuzaiful Md Yusof. The manuscript was drafted by Rachelle Steele (MedEvent Partners, London, UK) and managed by Vanessa Birardi (Aurinia, Rockville, MD, USA).

References

1 Mahajan A, Amelio J, Gairy K, et al. Systemic lupus erythematosus, lupus nephritis and end-stage renal disease: a pragmatic review mapping disease severity and progression. *Lupus* 2020; **29:** 1011–20.

2 Parikh SV, Almaani S, Brodsky S, Rovin BH. Update on lupus nephritis: core curriculum 2020. *Am J Kidney Dis* 2020; **76:** 265–81.

3 Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; **78:** 736–45.

4 Tamirou F, D'Cruz D, Sangle S, et al. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. *Ann Rheum Dis* 2016; **75:** 526–31.

5 Dall'Era M, Cisternas MG, Smilek DE, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol* 2015; **67:** 1305–13.

6 Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ, Collaborative Study Group. Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol* 2008; **3:** 46–53.

7 Tamirou F, Lauwerys BR, Dall'Era M, et al. A proteinuria cut-off level of 0·7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. *Lupus Sci Med* 2015; **2:** e000123.

8 Davidson JE, Fu Q, Ji B, et al. Renal remission status and longterm renal survival in patients with lupus nephritis: a retrospective cohort analysis. *J Rheumatol* 2018; **45:** 671–77.

9 Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med* 2020; **383:** 1117–28.

10 Zeher M, Doria A, Lan J, et al. Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis. *Lupus* 2011; **20:** 1484–93.

11 Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009; **20:** 1103–12.

12 Dall'Era M, Solomons N, Federico R, Truman M. Comparison of standard of care treatment with a low steroid and mycophenolate mofetil regimen for lupus nephritis in the ALMS and AURA studies. *Lupus* 2019; **28:** 591–96.

13 Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012; **64:** 1215–26.

14 Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis. *Ann Intern Med* 2015; **162:** 18–26.

15 Bao H, Liu Z-H, Xie H-L, Hu W-X, Zhang H-T, Li L-S. Successful treatment of class V+ IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 2008; **19:** 2001–10.

16 Busque S, Cantarovich M, Mulgaonkar S, et al. The PROMISE study: a phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation. *Am J Transplant* 2011; **11:** 2675–84.

17 Hošková L, Málek I, Kopkan L, Kautzner J. Pathophysiological mechanisms of calcineurin inhibitor-induced nephrotoxicity and arterial hypertension. *Physiol Res* 2017; **66:** 167.

18 van Gelder T, Huizinga RB, Lisk L, Solomons N. Voclosporin: a novel calcineurin inhibitor without impact on mycophenolic acid in patients with SLE. *Nephrol Dial Transplant* 2021; published online Feb 2. https://doi.org/10.1093/ndt/gfab022.

19 Rovin BH, Solomons N, Pendergraft WF 3rd, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int* 2019; **95:** 219–31.

20 Ruiz-Irastorza G, Danza A, Perales I, et al. Prednisone in lupus nephritis: how much is enough? *Autoimmunity Rev* 2014; **13:** 206–14.

21 Al Sawah S, Zhang X, Zhu B, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus—the Hopkins Lupus Cohort. *Lupus Sci Med* 2015; **2:** e000066.

22 Dooley MA, Hogan S, Jennette C, Falk R, for the Glomerular Disease Collaborative Network. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. *Kidney Int* 1997; **51:** 1188–95.

23 Contreras G, Lenz O, Pardo V, et al. Outcomes in African Americans and Hispanics with lupus nephritis. *Kidney Int* 2006; **69:** 1846–51.

24 Wang S, Li X, Qu L, et al. Tacrolimus versus cyclophosphamide as treatment for diffuse proliferative or membranous lupus nephritis: a non-randomized prospective cohort study. *Lupus* 2012; **21:** 1025–35.

25 Chen W, Tang X, Liu Q, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. *Am J Kidney Dis* 2011; **57:** 235–44.

26 Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. *Nephrol Dial Transplant* 2012; **27:** 1467–72.

27 Zavada J, Pešickova S, Ryšava R, et al. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study. *Lupus* 2010; **19:** 1281–89.

28 Kolic J, Beet L, Overby P, et al. Differential effects of voclosporin and tacrolimus on insulin secretion from human islets. *Endocrinology* 2020; **161:** bqaa162.

29 Faul C, Donnelly M, Merscher-Gomez S, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008; **14:** 931–38.

30 Wakamatsu A, Fukusumi Y, Hasegawa E, et al. Role of calcineurin (CN) in kidney glomerular podocyte: CN inhibitor ameliorated proteinuria by inhibiting the redistribution of CN at the slit diaphragm. *Physiol Rep* 2016; **4:** e12679.

31 Mathieson PW. The podocyte cytoskeleton in health and in disease. *Nephrol Dial Transplant Plus* 2012; **5:** 498–501.

32 Rovin B, Furie R, Aroca G, et al. B-cell depletion and response in a randomized, controlled trial of obinutuzumab for proliferative lupus nephritis. *Kidney Int Rep* 2020; **5:** S352.