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Safety and Efficacy of Long-Term Voclosporin Treatment for Lupus Nephritis in the Phase 3 AURORA 2 Clinical Trial

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Objective. AURORA 2 evaluated the long-term safety, tolerability, and efficacy of voclosporin compared to placebo in patients with lupus nephritis (LN) receiving an additional two years of treatment following completion of the one-year AURORA 1 study.

Methods. Enrolled patients continued their double-blinded treatment of voclosporin or placebo randomly assigned in AURORA 1, in combination with mycophenolate mofetil and low-dose glucocorticoids. The primary objective was safety assessed with adverse events (AEs) and biochemical and hematological assessments. Efficacy was measured by renal response.

Results. A total of 216 patients enrolled in AURORA 2. Treatment was well tolerated with 86.1% completing the study and no unexpected safety signals. AEs occurred in 86% and 80% of patients in the voclosporin and control groups, respectively, with an AE profile similar to that seen in AURORA 1, albeit with reduced frequency. Investigator reported AEs of both glomerular filtration rate (GFR) decrease and hypertension occurred more frequently in the voclosporin than the control group (10.3% vs 5.0%, and 8.6% vs 7.0%, respectively). Mean corrected estimated GFR (eGFR) was within the normal range and stable in both treatment groups. eGFR slope over the two-year period was –0.2 mL/min/1.73 m^2 (95% confidence interval [CI] –3.0 to 2.7) in the voclosporin group and –5.4 mL/min/1.73 m^2 (95% CI –8.4 to –2.3) in the control group. Improved proteinuria persisted across three years of treatment, leading to more frequent complete renal responses in patients treated with voclosporin (50.9% vs 39.0%; odds ratio 1.74; 95% CI 1.00–3.03).

Conclusion. Data demonstrate the safety and efficacy of long-term voclosporin treatment over three years of follow-up in patients with LN.

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The aggregated 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 a data access agreement is signed. Data will be available at the time of publication and for a minimum of five years from the end of the trial.

Author disclosures and a graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/art.42657.

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INTRODUCTION

Lupus nephritis (LN) occurs in up to 50% of patients with systemic lupus erythematosus (SLE) (1, 2). Compared to the general population, mortality risk is increased six- to nine-fold in patients with LN and 14- to 26-fold in patients with SLE with renal damage; thus, improved disease management to slow or stop progression to end-stage kidney disease is essential (3, 4). Proteinuria is a defining characteristic of chronic kidney disease and is independently associated with increased risk of mortality, myocardial infarction, and progression to kidney failure (5, 6). Unsurprisingly, reductions in proteinuria are associated with improved long-term outcomes. LN treatment guidelines recommend a target proteinuria level <0.5–0.7 g/24 hours and to allow a window in the first year of treatment to achieve this. Achieving early proteinuria reductions remains challenging with current immunomodulatory therapies (5, 7).

Voclosporin is a novel calcineurin inhibitor (CNI) approved in the United States and, more recently in Europe, for the treatment of adult patients with active LN in combination with background immunosuppression. Voclosporin is associated with a favorable metabolic profile with regard to lipids and glucose and a predictable pharmacokinetic profile resulting in no need for the therapeutic drug monitoring required of other CNIs (8–11). In AURORA 1, a 12-month, phase 3, double-blind, randomized-controlled pivotal study, the efficacy and safety of voclosporin was compared to placebo in achieving complete renal response (CRR) in patients with LN. AURORA 1 demonstrated the clinical superiority of voclosporin with mycophenolate mofetil (MMF) and low-dose glucocorticoids compared to MMF and low-dose glucocorticoids alone. Significantly more patients in the voclosporin group achieved a CRR at 52 weeks of treatment than those in the control group (12). The safety profile in AURORA 1 was comparable between treatment groups, in line with previous studies, and no new safety concerns were observed (8, 13–15).

The primary objective of AURORA 2 was to expand understanding of the safety of voclosporin, addressing questions on longer-term CNI effects, following the consistent efficacy demonstrated in earlier studies for the treatment of LN (8, 12).

We present results from the continued double-blind, phase 3 study, AURORA 2, assessing long-term safety and tolerability of voclosporin compared to placebo in patients with LN receiving an additional 24 months of treatment following completion of AURORA 1. Together, AURORA 1 and 2 represent the largest placebo-controlled clinical program evaluating a CNI-based treatment regimen for LN and the longest, as the only clinical trial to include three years of continuous LN treatment in combination with MMF and low-dose glucocorticoids.

PATIENTS AND METHODS

Trial design. AURORA 2 (EudraCT 2016-004046-28, Clinicaltrials.gov NCT03597464) was a phase 3, international, multicenter, double-blind, 24-month continuation study enrolling patients who completed 12 months of treatment in AURORA 1. This study complied with the International Council for Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The trial was conducted at 100 sites in 24 countries in North America, Latin America, Europe, South Africa, and Asia. The protocol was approved by the institutional review board or independent ethics committee at each trial site; all participants provided informed consent (Supplementary Methods, http://onlinelibrary.wiley.com/doi/10.1002/art.42657).

Patient entry criteria. Main inclusion criteria for AURORA 2 were provision of written informed consent, completion of study treatment in AURORA 1, and, in the opinion of the investigator, required use of continued immunosuppressive therapy.

Procedures. Patients enrolled in AURORA 2 continued to receive the same double-blind study treatment assigned by randomization in AURORA 1. Patient disposition details from AURORA 1 and 2 can be found in Supplementary Figure S1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42657. Patients, investigators, and the sponsor remained masked to the randomization assignment. Patients received study drug (voclosporin or matching placebo) at the same dose used at the end of AURORA 1 for an additional 24 months (up to month 36) in AURORA 2. Study drug dose modifications were allowed in AURORA 2 per investigator discretion. The protocol provided guidance to interrupt or reduce study drug for any patient with >30% decrease in estimated glomerular filtration rate (eGFR) or in the case of blood pressure, outside of acceptable limits (Supplementary Methods, http://onlinelibrary.wiley.com/doi/10.1002/art.42657). All patients continued to receive background standard of care with MMF and glucocorticoids at the same doses used at the end of AURORA 1 (12).

Outcomes. The primary objective of AURORA 2 was to assess the long-term safety and tolerability of voclosporin compared to placebo in patients with LN that completed one year of treatment in AURORA 1. Evaluation of safety included assessments of adverse events (AEs) and biochemical and hematological laboratory assessments during the study. An Independent Data and Safety Monitoring Board provided ongoing safety data review. Efficacy was assessed by achievement of CRR and partial renal response (PRR), good renal outcome, renal and non-renal flare, and changes in urine protein creatinine ratio (UPCR), eGFR, and serum creatinine (sCr).

Statistical analysis. Safety and efficacy analyses included all patients enrolled in AURORA 2. Analyses included data

available from the pretreatment baseline of AURORA 1 (ie, last value before patient received first dose of study drug on day 1 of AURORA 1) to end of follow-up in AURORA 2, including a safety visit at four weeks after study drug (voclosporin or placebo) discontinuation (ie, up to a total of 37 months follow-up inclusive of 12 months in AURORA 1 and 25 months in AURORA 2).

Laboratory values and vital signs were summarized monthly. AEs were reported using preferred terms (PT), based on investigator clinical judgement and discretion, aggregated by system organ class (SOC), and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

Efficacy was analyzed using a logistic regression model and had terms for treatment, pretreatment baseline UPCR, biopsy class, and MMF use at pretreatment baseline and region. CRR was defined as UPCR of ≤0.5 mg/mg, eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from pretreatment baseline in eGFR of >20%, received no rescue medication for LN, and received no more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during the eight weeks prior to the endpoint assessment. PRR was defined as a ≥50% reduction in UPCR from AURORA 1 pretreatment baseline. Patients withdrawing early from the study were counted as nonresponders in the assessment of CRR and PRR.

Good renal outcome was defined based on achievement of an adequate response and without renal flare. Adequate response was considered a sustained UPCR reduction ≤0.7 mg/mg, adjudicated by the blinded Clinical Endpoints Committee (CEC). Renal flares were analyzed in patients who achieved an adequate response and defined as an increase to UPCR >1 mg/mg from a post-response UPCR of <0.2 mg/mg or an increase to UPCR >2 mg/mg from a postresponse UPCR of 0.2 to 1.0 mg/mg, adjudicated by the blinded CEC. Non-renal flares were defined based on AEs, laboratory abnormalities and/or any other information presented, adjudicated by the blinded CEC. Laboratory-confirmed eGFR decrease ≥30% from AURORA 1 pretreatment baseline was confirmed by two consecutive study visits; pretreatment baseline was defined as the last value before patient received the first dose of the study drug on day 1 of AURORA 1.

Results are expressed as an odds ratio (OR) and associated two-sided 95% confidence interval (CI) for voclosporin compared to control. For CRR and PRR, OR >1 indicates benefit of voclosporin treatment; for good renal outcome, renal flare, and nonrenal flare, an OR <1 indicates benefit of voclosporin treatment.

Change from pretreatment baseline (AURORA 1 baseline) analyses used a mixed effect model repeated measures (MMRM) analysis. eGFR analyses used a corrected eGFR with all eGFR values higher than 90 mL/min/1.73 m^2 constrained to 90 mL/min/1.73 m^2.

For the purposes of this continuation study, no additional power or sample size calculations were performed. Details of the original power calculation performed for AURORA 1 have been reported previously (see Supplementary Methods, http://onlinelibrary.wiley.com/doi/10.1002/art.42657) (12).

RESULTS

Trial population. Of the 357 patients enrolled in AURORA 1, 255 completed treatment and were eligible for enrolment in AURORA 2. Between September 2019 and October 2021, 216 of the 255 (84.7%) treatment completers enrolled into AURORA 2; 116 in the voclosporin group and 100 in the control group. Of these, 101 in the voclosporin and 85 in the control group completed the study (Supplementary Figure S1, http://onlinelibrary.wiley.com/doi/10.1002/art.42657). Pretreatment baseline clinical characteristics and demographics were generally balanced between treatment groups except for an increased proportion of Black patients in the voclosporin group (15.5% voclosporin; 7.0% control). Pretreatment baseline corrected mean eGFR was similar between groups (79.0 mL/min/1.73 m^2 voclosporin; 78.7 mL/min/1.73 m^2 control) (Table 1).

In AURORA 2, patients continued on the same dose of the study drug used at the end of AURORA 1; the majority (78.4% voclosporin; 90.0% control) were receiving 23.7 mg twice daily (BID) voclosporin or equivalent placebo. At the end of AURORA 2, 49.1% of the voclosporin and 64.0% of the control group were receiving 23.7 mg BID of voclosporin or equivalent placebo (Supplementary Table S1, http://onlinelibrary.wiley.com/doi/10.1002/art.42657). Study drug dose changes decreased over time; the majority of patients were on a lowered dose at end of study, including more patients in the voclosporin arm, and underwent dose changes due to changes in eGFR (Supplementary Tables S2 and S3, http://onlinelibrary.wiley.com/doi/10.1002/art.42657). Exposure to MMF was similar between groups (mean ± SD daily dose of 1.9 ± 0.4 g/day in both groups). The majority (>75%) of patients in both groups at the end of AURORA 2 had maintained glucocorticoid tapering throughout and were receiving prednisone (or equivalent) doses ≤2.5 mg/day (Supplementary Table S4, http://onlinelibrary.wiley.com/doi/10.1002/art.42657).

Safety. Voclosporin was well tolerated over three years with no new or unexpected safety signals. In the AURORA 2 study period, the proportion of patients experiencing AEs was comparable between groups (86.2% in the voclosporin group; 80.0% in the control group), as was the incidence of serious AEs (SAEs) (18.1% in the voclosporin group; and 23.0% in the control group). The overall profile of AEs in the AURORA 2 treatment period was similar to that in the first year of treatment in AURORA 1; however, the frequency of AEs decreased each year. Of patients with AEs in AURORA 2, most (86.0% voclosporin; 81.3% control) had AEs that were mild or moderate in severity. Study drug discontinuation due to AEs occurred in 9.5% of the voclosporin and 17.0% of the control group.

Overall, across three years of treatment, infections were the most common type of AE by SOC (69.8% voclosporin; 72.0% control) with low rates of serious infection in both groups (12.9%

Table 1. Demographic and pretreatment baseline patient characteristics*

Patient characteristics	Voclosporin (n = 116)	Control (n = 100)
Age, mean ± SD, years	32.3 ± 10.3	35.4 ± 11.6
Sex, n (%)		
Female	105 (90.5)	88 (88.0)
Male	11 (9.5)	12 (12.0)
Race, n (%)		
White	44 (37.9)	40 (40.0)
Asian	30 (25.9)	30 (30.0)
Black	18 (15.5)	7 (7.0)
Other	24 (20.7)	23 (23.0)
Ethnicity, n (%)		
Hispanic or Latino	39 (33.6)	33 (33.0)
Non-Hispanic or non-Latino	77 (66.4)	67 (67.0)
Region, n (%)		
North America	15 (12.9)	9 (9.0)
Latin America	34 (29.3)	27 (27.0)
Europe and South Africa	38 (32.8)	37 (37.0)
Asia-Pacific	29 (25.0)	27 (27.0)
Biopsy class, n (%)		
Class III	14 (12.1)	21 (21.0)
Class IV	64 (55.2)	37 (37.0)
Class V	17 (14.7)	14 (14.0)
Mixed Class V and III/IV	21 (18.1)	28 (28.0)
Biopsy within 6 months of AURORA 1 screening, n (%)	100 (86.2)	90 (90.0)
Corrected eGFR, mean ± SD, mL/min/1.73 m^2	79.0 ± 15.1	78.7 ± 16.6
UPCR, mean ± SD, mg/mg	3.94 ± 2.6	3.87 ± 2.5
Time since initial LN diagnosis, mean ± SD, years	4.8 ± 5.3	5.0 ± 5.2
Time since initial SLE diagnosis, mean ± SD, years	6.6 ± 6.7	7.3 ± 6.9

* Pretreatment baseline defined as the last value before patient received first dose of study drug on Day 1 of AURORA 1. eGFR = estimated glomerular filtration rate; LN = lupus nephritis; SLE = systemic lupus erythematosus; UPCR = urine protein creatinine ratio.

voclosporin, 17.0% control) (Table 2). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection occurred in 7 patients in the voclosporin group and 12 patients in the control group; these events were serious in 2 patients in the voclosporin group and 5 patients in the control group (Supplementary Table S2, http://onlinelibrary.wiley.com/doi/10.1002/art.42657).

In AURORA 2, the AE GFR decreased (PT reported per investigator discretion) occurred in 12 (10.3%) patients in the voclosporin group and in 5 (5.0%) patients in the control group. Hypertension (PT reported per investigator discretion) occurred in 10 (8.6%) patients in the voclosporin group and 7 (7.0%) patients in the control group. Antihypertensive treatment was initiated in AURORA 2 in 3 (2.6%) patients in the voclosporin arm, and 10 (10.0%) patients in the control arm. Overall, AE rates, including GFR decrease and hypertension, were lower in AURORA 2 compared to those reported the first year of treatment in AURORA 1 (Supplementary Table S5, http://onlinelibrary.wiley.com/doi/10.1002/art.42657).

Mean levels of blood pressure, sCr, glucose, hemoglobin A1c, and lipids were stable over time in both groups (Supplementary Figures S2–S5; Supplementary Table S8, http://onlinelibrary.wiley.com/doi/10.1002/art.42657). Mean levels of potassium and magnesium remained within normal ranges (Supplementary Figures S6 and S7, http://onlinelibrary.wiley.com/doi/10.1002/art.42657).

Improvements in Safety of Estrogens in Lupus Erythematosus: National Assessment Version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) scores, complement 3 (C3), complement 4 (C4), and anti–double-stranded DNA (anti-dsDNA) were similar to previously reported outcomes in AURORA 1 (Supplementary Table S9, http://onlinelibrary.wiley.com/doi/10.1002/art.42657).

Four patients, all in the control group, died during the study; three deaths occurred during the study treatment period (due to SARS-CoV-2 infection in two patients and pulmonary embolism in one patient) and one death during the follow-up period (SARS-CoV-2 infection). No deaths were considered by the investigator to be related to study treatment.

Renal function by eGFR. Mean corrected eGFR remained in the normal range and stable over the study period in both treatment groups and was not statistically different between groups over the three-year treatment period (Figure 1; Supplementary Table S6, http://onlinelibrary.wiley.com/doi/10.1002/art.42657). At pretreatment baseline, mean corrected eGFR slope was 79.0 and 78.7 mL/min/1.73 m^2 in the voclosporin and control groups, respectively, whereas at month 36, the respective measurements were 80.3 and 78.7 mL/min/1.73 m^2. Long-term renal function was evaluated with an eGFR slope over the 24-month period in AURORA 2, considering the expected acute and early changes in eGFR that occurred in the first year of treatment in AURORA 1. As such, from 12 months exposure onwards, the corrected eGFR slope during AURORA 2 was –0.2 mL/min/1.73 m^2 (95% CI –3.0 to 2.7) in the voclosporin group and –5.4 mL/min/1.73 m^2 (95% CI –8.4 to –2.3) in the control group (Figure 2; Supplementary Table S7, http://onlinelibrary.wiley.com/doi/10.1002/art.42657).

A laboratory-confirmed ≥30% decrease in corrected eGFR from pretreatment baseline was reported in 14 (12.1%) patients in the voclosporin group and 10 (10%) patients in the control group over the three-year treatment period (Table 3).

Renal efficacy. Reductions in mean UPCR achieved during the first year of treatment in AURORA 1 (voclosporin, 0.86 mg/mg; control, 1.47 mg/mg) were maintained over the AURORA 2 study period in both groups. MMRM analysis confirmed significantly greater reductions from baseline in UPCR were achieved in the voclosporin group compared with the control group at all time points except month 36. At the follow-up safety visit, mean UPCR was 0.78 mg/mg in the voclosporin group and 1.47

Table 2. Adverse events by year of study*

Adverse events	Voclosporin (n = 116)					Control (n = 100)				
	Year 1 (n = 116)	Year 2 (n = 116)	Year 3 (n = 103)	Overall three-year treatment period (n = 116)	AURORA 2 only (n = 116)	Year 1 (n = 100)	Year 2 (n = 100)	Year 3 (n = 85)	Over all three-year treatment period (n = 100)	AURORA 2 only (n = 100)
AE, n (%)	103 (88.8)	85 (73.3)	67 (65.0)	107 (92.2)	100 (86.2)	84 (84.0)	66 (66.0)	46 (54.1)	95 (95.0)	80 (80.0)
Treatment-related AE, n (%)	47 (40.5)	21 (18.1)	9 (8.7)	58 (50.0)	28 (24.1)	20 (20.0)	18 (18.0)	8 (9.4)	31 (31.0)	21 (21.0)
SAE, n (%)	13 (11.2)	13 (11.2)	8 (7.8)	31 (26.7)	21 (18.1)	13 (13.0)	18 (18.0)	8 (9.4)	28 (28.0)	23 (23.0)
Treatment-related SAE, n (%)	4 (3.4)	1 (0.9)	0	5 (4.3)	1 (0.9)	2 (2.0)	2 (2.0)	0	4 (4.0)	2 (2.0)
AEs by SOC (reported in ≥15% of patients in either group)										
Infections and infestations, n (%)	70 (60.3)	45 (38.8)	35 (34.0)	81 (69.8)	57 (49.1)	60 (60.0)	30 (30.0)	21 (24.7)	72 (72.0)	43 (43.0)
Gastrointestinal disorders, n (%)	51 (44.0)	21 (18.1)	13 (12.6)	56 (48.3)	28 (24.1)	29 (29.0)	11 (11.0)	7 (8.2)	36 (36.0)	15 (15.0)
Musculoskeletal connective tissue disorders, n (%)	26 (22.4)	18 (15.5)	13 (12.6)	41 (35.3)	27 (23.3)	27 (27.0)	13 (13.0)	10 (11.8)	40 (40.0)	23 (23.0)
Investigations, n (%)†	30 (25.9)	19 (16.4)	8 (7.8)	43 (37.1)	24 (20.7)	16 (16.0)	11 (11.0)	5 (5.9)	29 (29.0)	16 (16.0)
Nervous system disorders, n (%)	33 (28.4)	11 (9.5)	5 (4.9)	40 (34.5)	14 (12.1)	13 (13.0)	6 (6.0)	3 (3.5)	17 (17.0)	8 (8.0)
Skin and subcutaneous tissue disorders, n (%)	26 (22.4)	13 (11.2)	12 (11.7)	38 (32.8)	21 (18.1)	16 (16.0)	6 (6.0)	4 (4.7)	20 (20.0)	9 (9.0)
Blood and lymphatic system disorders, n (%)	23 (19.8)	6 (5.2)	12 (11.7)	31 (26.7)	16 (13.8)	16 (16.0)	5 (5.0)	5 (5.9)	22 (22.0)	9 (9.0)
Vascular disorders, n (%)	25 (21.6)	7 (6.0)	3 (2.9)	31 (26.7)	10 (8.6)	12 (12.0)	8 (8.0)	5 (5.9)	24 (24.0)	13 (13.0)
General disorders and administration site conditions, n (%)	19 (16.4)	11 (9.5)	7 (6.8)	29 (25.0)	14 (12.1)	19 (19.0)	4 (4.0)	8 (9.4)	24 (24.0)	13 (13.0)
Renal and urinary disorders, n (%)	11 (9.5)	13 (11.2)	9 (8.7)	27 (23.3)	21 (18.1)	8 (8.0)	6 (6.0)	5 (5.9)	15 (15.0)	10 (10.0)
Metabolism and nutrition disorders, n (%)	11 (9.5)	4 (3.4)	7 (6.8)	20 (17.2)	12 (10.3)	19 (19.0)	6 (6.0)	1 (1.2)	22 (22.0)	8 (8.0)
Respiratory, thoracic, and mediastinal disorders, n (%)	14 (12.1)	7 (6.0)	3 (2.9)	19 (16.4)	9 (7.8)	8 (8.0)	5 (5.0)	1 (1.2)	13 (13.0)	6 (6.0)
Injury, poisoning and procedural complications, n (%)	10 (8.6)	7 (6.0)	10 (9.7)	18 (15.5)	15 (12.9)	8 (8.0)	9 (9.0)	1 (1.2)	13 (13.0)	9 (9.0)

* Data reported are n (%). AEs reported for events in AURORA 1 and AURORA 2 and up to 30 days after study treatment end. Patients are counted once within a SOC and once for each unique PT. AEs were aggregated by SOC and PT and coded using MedDRA version 20.0. Abbreviations: AE, adverse event; eGFR, estimated glomerular filtration rate; MeDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SOC, system organ class.
† The SOC of Investigations is driven by AEs of GFR decrease (Overall, voclosporin, n = 28 [24.1%], 47 events; control, n = 9 [9.0%], 13 events).

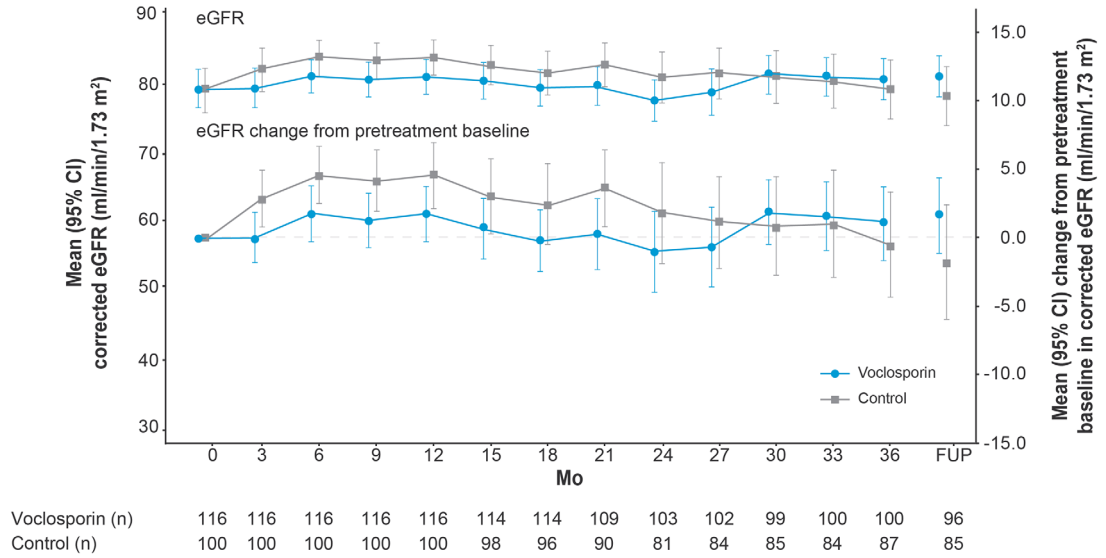

Figure 1. Mean corrected eGFR (95% CI) and mean change from pretreatment AURORA 1 baseline. Analysis of AURORA 2 patients (n = 216) includes pooled data from AURORA 1 and AURORA 2, including a FUP visit at four weeks after study drug discontinuation. Pretreatment baseline was defined as the last value before patient received first dose of study drug on day 1 of AURORA 1. CI, confidence interval; eGFR, estimated glomerular filtration rate; FUP, follow-up.

mg/mg in the control group (Figure 3A). Overall, the proportions of patients achieving ≥50% reduction from baseline in UPCR and UPCR ≤0.5 mg/mg increased up to months 12 and 18 and were maintained over the total treatment period (Figure 3B; Supplementary Figure S8, http://onlinelibrary.wiley.com/doi/10.1002/art.42657).

There was a significant improvement in CRR and PRR with voclosporin treatment compared to control at nearly every time point. At the end of AURORA 2 (month 36), more patients in the voclosporin group than in the control group achieved a CRR (50.9% vs 39.0%; OR 1.74; 95% CI 1.00–3.03), largely driven by achieving a proteinuria reduction in UPCR ≤0.5 mg/mg (54.3% vs 43.0%; OR 1.66; 95% CI 0.96–2.88), and achieved a PRR (74.1% vs 69.0%; OR 1.39; 95% CI 0.75–2.58) (Table 3; Supplementary Table S10, http://onlinelibrary.wiley.com/doi/10.1002/art.42657). In a last observation carried forward analysis of patients without data at month 36, 12 of 17 (70.6%) patients in the voclosporin group and 5 of 13 (38.5%) patients in the control group achieved ≥50% reduction from baseline in UPCR based on their final UPCR measurement.

Overall, significantly more patients in the voclosporin group than in the control group achieved a good renal outcome (66.4% vs 54.0%; OR 0.56; 95% CI 0.32–0.99), that is, an adequate response with UPCR ≤0.7 mg/mg and no subsequent renal flare, as adjudicated by the blinded CEC. Of patients who achieved adequate response (101 in the voclosporin group; 73 in the

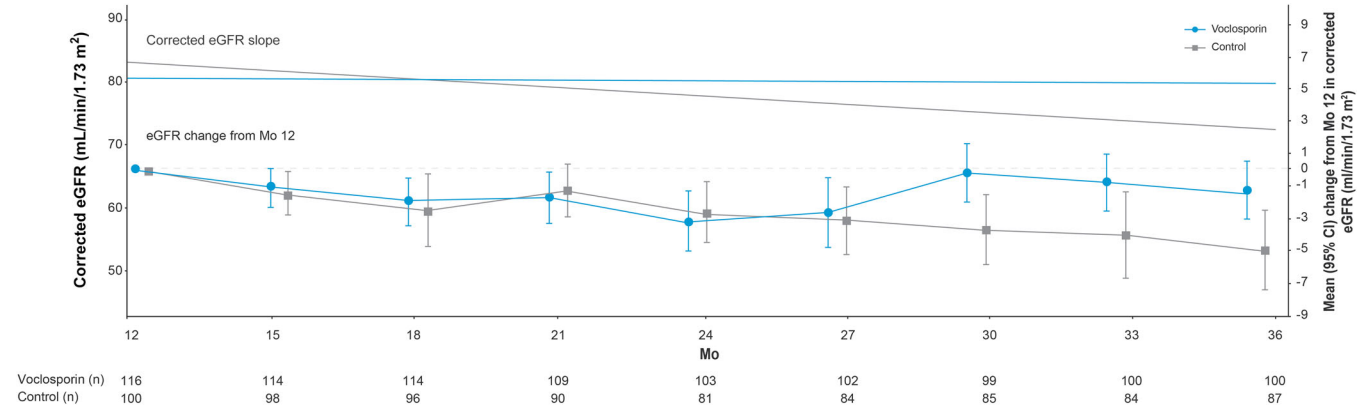

Figure 2. LS mean slopes of corrected eGFR and eGFR change (95% CI) from month 12. AURORA 2 patients (n = 216) completed 12 months of treatment in AURORA 1 before entering AURORA 2. Mean corrected eGFR slope and eGFR change are calculated from entry into AURORA 2 (month 12 of treatment) to end of AURORA 2 at month 36. CI, confidence interval; LS mean, least squares mean; eGFR, estimated glomerular filtration rate.

Table 3. Efficacy analyses*

Analyses	Voclosporin (n = 116), % (n/n)	Control (n = 100), % (n/n)	OR (95% CI)	*P* value
CRR				
Month 12	52.6 (61/116)	34.0 (34/100)	2.30 (1.30–4.05)	0.004
Month 24	56.0 (65/116)	43.0 (43/100)	1.81 (1.04–3.16)	0.035
Month 36	50.9 (59/116)	39.0 (39/100)	1.74 (1.00–3.03)	0.051
PRR				
Month 12	89.7 (104/116)	70.0 (70/100)	3.99 (1.88–8.46)	<0.001
Month 24	77.6 (90/116)	58.0 (58/100)	2.68 (1.46–4.91)	0.001
Month 36	74.1 (86/116)	69.0 (69/100)	1.39 (0.75–2.58)	0.290
Proportion with ≤0.5 mg/mg UPCR				
Month 12	54.3 (63/116)	34.0 (34/100)	N/A	N/A
Month 24	65.7 (69/105)	54.3 (44/81)	N/A	N/A
Month 36	63.6 (63/99)	49.4 (43/87)	N/A	N/A
Proportion with ≥50% UPCR reduction from baseline				
Month 12	89.7 (104/116)	70.0 (70/100)	N/A	N/A
Month 24	85.7 (90/105)	71.6 (58/81)	N/A	N/A
Month 36	86.9 (86/99)	79.3 (69/87)	N/A	N/A
Proportion with ≥30% eGFR decrease overall	12.1 (14/116)	10.0 (10/100)	N/A	N/A
Good renal outcome overall	66.4 (77/116)	54.0 (54/100)	0.56 (0.32–0.99)	0.045
Renal flare overall	23.8 (24/101)	26.0 (19/73)	0.85 (0.42–1.73)	0.662
Non-renal flare overall	18.1 (21/116)	14.0 (14/100)	1.33 (0.63–2.81)	0.448

* Analysis of AURORA 2 patients (n=216) includes pooled data from AURORA 1 and AURORA 2. Values of proportion data are percentages calculated with the denominator representing the number of patients contributing data at each time point. Patients who withdrew from the study prior to the response assessment or did not have data at the specified timepoint were defined as non-responders in CRR and PRR assessments. Abbreviations: AE, adverse event; CEC, Clinical Endpoints Committee; CI, confidence interval; CRR, complete renal response; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; MMF, mycophenolate mofetil; N/A, not applicable; OR, odds ratio; PRR, partial renal response; UPCR, urine protein creatinine ratio.

control group), similar proportions in each group experienced renal flares. Non-renal flares were also similar in each group over the three-year treatment period (Table 3).

DISCUSSION

AURORA 2 demonstrates the safety and tolerability of continued administration of voclosporin over three years of treatment in patients with LN; voclosporin was well tolerated with no new or worsening safety signals and with stability of renal function. Clinical efficacy over three years of treatment was maintained, as observed by continued reduced UPCR, increased CRR, and preserved kidney function, suggesting a positive benefit-risk profile for voclosporin in patients with LN.

AURORA 2 was a phase 3, two-year, double-blinded, placebo-controlled continuation trial of the pivotal AURORA 1 study. More than 80% of patients who completed treatment in

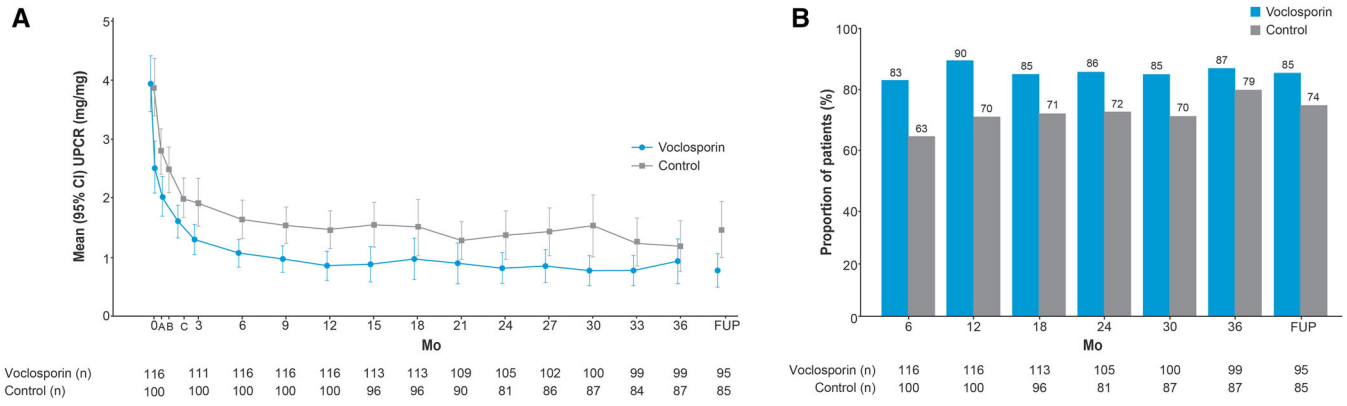

Figure 3. Mean UPCR (95% CI) and proportion of patients with 50% reduction in UPCR from baseline. Analysis of AURORA 2 patients (n = 216) includes pooled data from AURORA 1 and AURORA 2, including a FUP at four weeks after study drug discontinuation. (a) Mean UPCR data of patients by study visit. (**A**) indicates two weeks from the start of study treatment. (**B**) indicates four weeks from the start of study treatment. (**C**) indicates eight weeks from the start of study treatment. (b) Proportion of patients with at least a 50% reduction from baseline in UPCR by visit. Percentages calculated with denominator that includes patients with a UPCR measure at the specified timepoint. Patients without data at the timepoint are not included. Baseline defined as last value before patient received first dose of study drug on day 1 of AURORA 1. CI, confidence interval; FUP, follow-up visit; UPCR, urine protein creatinine ratio.

AURORA 1 continued in AURORA 2. Key baseline characteristics were balanced between groups. As such, AURORA 2 is structured to provide valuable information on the long-term benefit and risk of voclosporin treatment in adults with LN.

Overall adverse event profiles in AURORA 2 of voclosporin and control groups were comparable, with AEs declining annually and few patients discontinuing due to AEs, suggesting that long-term voclosporin is well tolerated. Adverse events associated with the hemodynamic effects of the CNI drug class, such as hypertension and GFR decrease, occurred more often in the voclosporin group, yet decreased over time, and were managed through dose modifications. There were very few events of Type 2 diabetes mellitus, hyperkalemia, or hyperlipidemia in either group over the course of the study, consistent with earlier reports of improved glucose, electrolyte, and lipid profiles with the voclosporin treatment regimen relative to earlier generation calcineurin inhibitors (12, 14). Furthermore, drug discontinuations were less frequent in the voclosporin group compared with the control group. Unique pharmacokinetic–pharmacodynamic properties, including the low metabolite load and eGFR-based dosing of voclosporin, are likely responsible for the benign safety profile observed with voclosporin (11, 16–18).

Significantly more patients in the voclosporin group achieved CRR at the end of AURORA 1 and did so earlier than patients in the control group (12). Such timely renal response has previously been shown to lead to long-term kidney preservation (19, 20). Although an expected minor decrease in kidney function was observed early in AURORA 1 due to the hemodynamic renal effect of CNIs, data across three years of voclosporin exposure showed stable kidney function, as measured with mean eGFR and slope throughout the study (21). eGFR slope in the control group decreased slightly, likely reflecting the natural progression of LN, which has been similarly observed in other trials of LN (22, 23). Preservation of long-term kidney function along with the favorable safety results of AURORA 2 establishes a positive benefit–risk profile for voclosporin as part of standard of care LN treatment.

At the start of AURORA 2, mean UPCR was lower in the voclosporin (0.86 mg/mg) than in the control group (1.47 mg/mg), reflecting improved disease control by voclosporin in the first year of treatment. Additionally, more voclosporin patients had a good renal outcome than those in the control group, demonstrating a clear clinical benefit of voclosporin.

It is noteworthy that, for patients achieving adequate disease control, results were attained in a setting where study drug dose modifications were permitted; approximately 30% of the voclosporin group and 9% of the control group ended AURORA 2 on a lower dose. Most dose changes occurred in the first year of treatment in AURORA 1, potentially reflecting real-world clinical practice in terms of long-term safety, tolerability, and efficacy.

Patients in AURORA 2 continued the randomized treatment assignment of voclosporin or placebo from AURORA 1. Although AURORA 2 treatment groups were relatively balanced with respect to baseline demographic characteristics, more patients in the voclosporin group had achieved a renal response at the start of AURORA 2, and the mean UPCR level was lower in voclosporin patients, representing a potential source of selection bias for those patients choosing to enter AURORA 2 and a limitation of the study. As more patients in the voclosporin group both continued into AURORA 2 and achieved proteinuria reductions, more patients in this group were therefore assessed for renal flare. This should be borne in mind when comparing renal flare rates between groups; it may be helpful to refer to good renal outcome, which was assessed in all patients of the study, that is, the number of patients with adequate response (proteinuria reduction) and no renal flare. Continuation studies typically are open label, a potential source of bias avoided in this study as AURORA 2 continued as a double-blinded study. Voclosporin treatment data collection included results from AURORA 1, providing an opportunity to assess long-term effects of treatment durability and response and clinical parameters indicative of safety. As a long-term study occurring, in part, during the COVID-19 pandemic, it is notable that the majority of patients attended most study visits and completed three years of treatment. We also acknowledge in CRR and PRR analyses that patients who missed a study visit or discontinued early are considered non-responders. Therefore, it may be informative to evaluate efficacy outcomes with the descriptive analyses including only the proportion of patients contributing data at specified timepoints.

Preclinical work demonstrates that voclosporin inhibits SARs-CoV-2 replication, with clinical research in this area recently reported (24, 25). Interestingly, three deaths due to coronavirus infection occurred in the control group during AURORA 2 and none in the voclosporin group. Whether calcineurin suppression of cytokine production from immune cells or inhibition of SARs-CoV-2 replication could contribute to this observation merits further research.

This analysis confirms the safety, tolerability, and efficacy of voclosporin reported previously, with no new or unexpected safety signals observed with an additional two years of treatment. We propose that the rapid renal response achieved with voclosporin treatment has beneficial long-term consequences, supported by stable kidney function over the three-year treatment period. Overall, three-year data provides further support for the use of voclosporin with MMF and low-dose glucocorticoids for the treatment of LN.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Randhawa, Lisk, Huizinga.

Acquisition of data. Saxena, Ginzler, Gibson, Satirapoj, Zuta Santillán, Levchenko, Navarra, Atsumi, Yasuda, Chavez-Perez, Arriens, Parikh, Caster, Teng.

Analysis and interpretation of data. Saxena, Ginzler, Gibson, Satirapoj, Zuta Santillán, Levchenko, Navarra, Atsumi, Yasuda, Chavez-Perez, Arriens, Parikh, Caster, Birardi, Randhawa, Lisk, Huizinga, Teng.

ROLE OF THE STUDY SPONSOR

Aurinia Pharmaceuticals was involved in the study design and in the collection, analysis, and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. Publication of this article was contingent upon approval by Aurinia Pharmaceuticals.

REFERENCES

1. Tamirou F, Houssiau FA. Management of lupus nephritis. J Clin Med 2021;10:670.
2. 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. doi: https://doi.org/10.1177/0961203320932219
3. Kostopoulou M, Adamichou C, Bertsias G. An update on the diagnosis and management of lupus nephritis. Curr Rheumatol Rep 2020; 22:30.
4. Mok CC, Kwok RC, Yip PS. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. Arthritis Rheum 2013;65:2154–60.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int 2021;100:S1–276.
6. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010;303:423–9.
7. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis 2020;79:713–23.
8. 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.
9. Kolic J, Beet L, Overby P, et al. Differential effects of voclosporin and tacrolimus on insulin secretion from human islets. Endocrinology 2020;161(11):bqaa162.
10. Van Gelder T, Huizinga R, Noukens J, et al. Use of therapeutic drug monitoring does not add clinical value for voclosporin in patients with lupus nephritis. Paper presented at: ASN's Kidney Week; October 22–25, 2020; virtual. https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3445407
11. van Gelder T, Lerma E, Engelke K, et al. Voclosporin: a novel calcineurin inhibitor for the treatment of lupus nephritis. Expert Rev Clin Pharmacol 2022;15:515–29.
12. Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2021;397:2070–80.
13. Naidoo P, Rambiritch V. Voclosporin (ISA247) for plaque psoriasis. Lancet 2008;372:888–9.
14. van Gelder T, Huizinga RB, Lisk L, et al. Voclosporin: a novel calcineurin inhibitor with no impact on mycophenolic acid levels in patients with SLE. Nephrol Dial Transplant 2022;37:917–22.
15. Rovin BH, Solomons N, Pendergraft WF, III, 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.
16. Li Y, Palmisano M, Sun D, et al. Pharmacokinetic disposition difference between cyclosporine and voclosporin drives their distinct efficacy and safety profiles in clinical studies. Clin Pharmacol 2020;12: 83–96.
17. Mayo PR, Huizinga RB, Ling SY, et al. Voclosporin food effect and single oral ascending dose pharmacokinetic and pharmacodynamic studies in healthy human subjects. J Clin Pharmacol 2013;53:819–26.
18. Ling SY, Huizinga RB, Mayo PR, et al. Pharmacokinetics of voclosporin in renal impairment and hepatic impairment. J Clin Pharmacol 2013;53:1303–12.
19. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 2004;50:3934–40.
20. Moroni G, Gatto M, Tamborini F, et al. Lack of EULAR/ERA-EDTA response at 1 year predicts poor long-term renal outcome in patients with lupus nephritis. Ann Rheum Dis 2020;79:1077–83.
21. Hošková L, Málek I, Kopkan L, et al. Pathophysiological mechanisms of calcineurin inhibitor-induced nephrotoxicity and arterial hypertension. Physiol Res 2017;66:167–80.
22. 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.
23. Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med 2020;382:211–21.
24. Arends EJ, Meziyerh S, Moes DJ, et al. Antiviral effects of voclosporin on SARS-CoV-2 in immunocompromised kidney patients. Kidney Int Rep 2023.
25. Ogando NS, Metscher E, Moes D, et al. The cyclophilin-dependent calcineurin inhibitor voclosporin inhibits SARS-CoV-2 replication in cell culture. Transpl Int 2022;35:10369.