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Update on the Efficacy and Safety Profile of Voclosporin: An Integrated Analysis of Clinical Trials in Lupus Nephritis

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Objective. This integrated analysis evaluates the efficacy and safety of voclosporin, a novel calcineurin inhibitor, at 23.7 mg twice daily in combination with mycophenolate mofetil (MMF) and oral glucocorticoids in lupus nephritis (LN) using pooled data from two large phase II and phase III clinical trials. The purpose was to expand the pool of patients for safety analyses and to increase power for efficacy analyses in patient subpopulations.

Methods. Aurinia Urinary Protein Reduction in Active Lupus with Voclosporin (AURA-LV) (phase II) and Aurinia Renal Response in Active Lupus With Voclosporin (AURORA 1) (phase III) were randomized, placebo-controlled, double-blind trials with similar designs and end points comparing voclosporin to control in combination with MMF and oral glucocorticoids for the treatment of LN. The primary efficacy outcome of the integrated analysis was complete renal response (CRR) at approximately one year (Week 48 data from AURA-LV and Week 52 from AURORA 1). Safety was assessed throughout the trials.

Results. Overall, 534 patients (268 voclosporin; 266 control) were included in the integrated analysis. Significantly more patients achieved a CRR at one year in the voclosporin group than in the control group (43.7% vs. 23.3%; OR 2.76; 95% CI 1.88, 4.05 $P < 0.0001$). The incidence of adverse events (AEs) was similar (91.4% voclosporin; 87.2% control). Most AEs were mild to moderate in severity; the most commonly reported AEs were classified as infections and infestations (62.2% voclosporin; 54.9% control) and gastrointestinal disorders (45.3% voclosporin; 35.3% placebo). No new or unexpected safety signals were detected.

Conclusions. This integrated analysis demonstrates the efficacy and safety of voclosporin in the treatment of LN across the diverse racial and ethnic groups studied.

INTRODUCTION

Lupus nephritis (LN) is a common and serious complication of systemic lupus erythematosus (SLE), affecting up to 60% of patients, and is the single most important predictor of morbidity, and a major cause of mortality in those with SLE (1–3). LN is a form of glomerulonephritis characterized by proteinuria and a potential decrease in kidney function (4). In up to 30% of patients, LN will progress to end-stage kidney disease (ESKD) within the first decade (5).

The goals of LN treatment include rapid remission of active disease and preservation of kidney function while minimizing treatment-related toxicity and improving disease-related quality of life (1,6). Reductions in proteinuria are associated with improved long-term renal outcomes in LN, and, for this reason, all measures of shorter-term treatment efficacy include a reduction in proteinuria as a key part of the response criteria (7–11). Recent treatment recommendations support target proteinuria decreases of at least 50% by 6 months and <0.5 to 0.7 gm/24 hours with a near normal glomerular filtration rate (GFR) by 12 months (6). However, up to

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SIGNIFICANCE & INNOVATIONS

- This integrated analysis, based on data from 534 patients, has permitted further exploration of the efficacy of voclosporin across various subpopulations, as well as a deeper investigation into the safety of this novel calcineurin inhibitor, allowing clinicians to better understand the positive benefit-risk profile of voclosporin in patients with Lupus nephritis (LN).
- Reductions in proteinuria are associated with improved long-term outcomes in LN; patients treated with voclosporin in combination with mycophenolate mofetil (MMF) and oral glucocorticoids achieved meaningful reductions in proteinuria more rapidly than patients treated with MMF and glucocorticoids alone.
- This analysis also supports the use of lower doses of glucocorticoids in the treatment of LN.

60% of LN patients do not meet these targets, and the incidence of ESKD due to LN has remained largely unchanged over the last few decades (6,7,10,12).

Treatment toxicity also remains a concern; although glucocorticoids are one of the mainstays of LN therapy, there are serious risks associated with their long-term use, and there is significant interest in treatment regimens that limit exposure to glucocorticoids while maintaining efficacy (13,14).

Voclosporin, a novel calcineurin inhibitor (CNI), has demonstrated a consistent pharmacokinetic and pharmacodynamic profile, eliminating the need for the therapeutic drug monitoring required for other CNIs (15). When administered in combination with mycophenolate mofetil (MMF), which is often used in the treatment of LN, voclosporin has been shown to have no effect on exposure to mycophenolic acid, the active moiety of MMF (16). Further, voclosporin is associated with a more favorable effect on lipid and glucose levels than that reported for other CNIs (17). Based on positive results from the pivotal phase II and III trials, voclosporin became the first oral therapy approved in the United States for adults with active LN.

The phase II Aurinia Urinary Protein Reduction in Active Lupus with Voclosporin (AURA-LV) and phase III Aurinia Renal Response in Active Lupus With Voclosporin (AURORA 1) studies make up the largest successful LN clinical program to date, enrolling a total of 534 patients (18,19). Similar in design and conducted in comparable patient populations, both trials demonstrated a clinically meaningful and statistically significant treatment benefit of adding 23.7 mg twice daily (BID) voclosporin to a background of MMF and glucocorticoids. The objective in combining these two datasets for this integrated analysis was to obtain a larger ethnically and racially diverse patient population than was previously available, allowing for a more in-depth analysis of safety outcomes and to increase the power of efficacy analyses in specific subpopulations.

PATIENTS AND METHODS

Study designs. Data were derived from phase II and phase III randomized, prospective, placebo-controlled, double-blind, multicenter, international, three-arm and two-arm comparison trials, respectively. (ClinicalTrials.gov and EudraCT identifiers: NCT02141672 and 2012-003364-51 [AURA-LV]; NCT03021499 and 2016-004045-81 [AURORA 1]). Study designs and methods of AURA-LV and AURORA 1 were similar and have been described elsewhere (18,19). For both studies, 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.

Participants. Patients in both studies were 18 years or older, diagnosed with active LN with a kidney biopsy result of class III, IV, or V (±III/IV) within six months (AURA-LV) or two years (AURORA 1) of enrollment, had proteinuria of ≥1.5 mg/mg (≥2 mg/mg for class V) by first morning void, had an estimated GFR (eGFR) of ≥45 ml/minute/1.73 m^2 at screening, and required immunosuppression in the opinion of the investigator. Patients were ineligible if their QT interval corrected for heart rate using Fridericia's Correction Formula (QTcF) exceeded 480 msec in the presence of a normal QRS interval (<110 msec) at screening.

Procedures. In AURA-LV, patients were randomly assigned (2:2:1:1) to one of four treatment groups: oral voclosporin (23.7 mg BID or 39.5 mg BID) or matched placebo in the control arm. In AURORA 1, patients were randomly assigned (1:1) to voclosporin 23.7 mg BID or matching placebo in the control arm. Data from the 23.7 mg BID dosing arms of voclosporin and all control arms of both studies were incorporated into this integrated analysis.

All patients received background MMF (2 gm per day) and glucocorticoids. Doses of MMF from 1 to 3 gm per day were permitted with approval of the medical monitor. Glucocorticoids were administered according to a protocol-defined tapering schedule (intravenous methylprednisolone on Days 1 and 2 and oral prednisone on Day 3, starting at 20–25 mg per day and decreasing to a low dose of ≤2.5 mg per day by Week 16) (additional steroid dosing details in Supplementary Text 1, available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.25007). Neither initiation nor dose modification within four weeks prior to randomization was allowed for angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors. If used prior to study entry, patients were allowed to continue at the same dose during the study to minimize the influence of ARB/ACE inhibitor therapy on outcomes; changing doses resulted in failure of the efficacy end point of complete renal response (CRR).

Because of the expected hemodynamic effects of CNIs on the kidney (17), study protocols provided guidance to interrupt or modify study treatment for patients experiencing decreases in eGFR or increases in blood pressure (Supplementary Text 1, available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.25007).

Outcomes. The primary efficacy measure for this integrated analysis was CRR at approximately one year of treatment, combining AURA-LV data at 48 weeks with AURORA 1 data at 52 weeks. CRR was defined as urine protein creatinine ratio (UPCR) ≤0.5 mg/mg, with an eGFR of ≥60 ml/minute/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20%, no administration of rescue medication, and no more than 10 mg per day prednisone equivalent for ≥3 consecutive days or for ≥7 days during the 8 weeks prior to efficacy assessment.

Additional efficacy analyses included CRR at six months, partial renal response (PRR) (≥50% reduction from baseline UPCR) at one year and six months, time to UPCR less than or equal to 0.5 mg/mg, and time to a ≥50% reduction in UPCR from baseline. Changes from baseline visit in UPCR, serum creatinine, and corrected eGFR and changes from screening visit in complement 3 (C3), complement 4 (C4) and anti-double-stranded deoxyribonucleic acid (anti-dsDNA) were also assessed. Safety analyses included adverse events (AEs), laboratory parameters, vital signs, electrocardiograms (ECGs), physical examination, and all events of death reported during study follow-up.

Statistical analysis. All analyses were performed using pooled data from the 23.7 mg BID voclosporin arms and all control arms following the statistical methodology of AURORA 1 (Supplementary Text 2).

Change from baseline measures used a mixed effect model repeated measures (MMRM) analysis. To account for baseline renal hyperfiltration, analyses of corrected eGFR (utilizing the Chronic Kidney Disease Epidemiology Collaboration equation) constrained all values greater than 90 ml/minute/1.73 m^2 to a maximum of 90 ml/minute/1.73 m^2.

Efficacy analyses included all randomized patients. Safety analyses included patients who received at least one dose of study drug (voclosporin or control). The studies were not powered to detect statistically significant differences based on demographic or baseline patient characteristics. All analyses were performed using SAS, version 9.4.

RESULTS

The integrated population consisted of 534 patients: 268 in the voclosporin group (89 from AURA-LV; 179 from AURORA 1) and 266 in the control group (88 from AURA-LV; 178 from AURORA 1). Except for one patient in the voclosporin group, all randomized patients received at least one dose of study treatment. Overall, 453 (84.8%) patients completed their respective studies (32 [11.9%] and 49 [18.4%] in the voclosporin and control groups withdrew early).

Between-group demographic and clinical characteristics were well-balanced (Table 1). The overall mean age was 33 years (range: 18-72 years); most patients were women (462 [86.5%]). There were approximately equal proportions of White (201 [37.6%]) and Asian patients (197 [36.9%]), with most Asian patients being from outside of the Indian subcontinent (157 [29.4%]). Approximately 10% of patients were Black, and 25% were Hispanic or Latino. ACE inhibitors or ARBs were used by 60.7% and 65.0% of the voclosporin and control groups at baseline, respectively (Table 1). Antimalarials were used by 59.2% and 57.5% of patients at screening, respectively.

Demographics were similar when examined by study, aside from a higher proportion of Hispanic or Latino patients enrolled into AURORA 1 than AURA-LV (32.5% vs. 12.4%) and a higher proportion of Asian patients enrolled in AURA-LV than AURORA 1 (49.7% vs. 30.5%). Baseline disease characteristics were also similar, although LN was diagnosed more recently in AURA-LV (0.9 years vs. 2.0 years). Mean ± SD baseline UPCR was balanced between the studies (AURA-LV: 4.8 ± 3.9 mg/mg; AURORA 1: 4.0 ± 2.5 mg/mg).

Overall, 70.6% of patients (73.1% and 68.0% in the voclosporin and control groups, respectively) completed the protocol-defined course of study treatment. Mean ± SD daily doses of voclosporin and placebo were 39.1 ± 11.5 mg per day and 48.3 ± 12.3 mg per day, respectively; the placebo dose was higher, as this group included the high-dose (39.5 mg BID placebo) control patients from AURA-LV. Mean ± SD duration of exposure to study drug was similar for both voclosporin- and control-treated patients (310 ± 102.2 vs. 304 ± 101.4 days, respectively). Similar proportions of patients achieved the per-protocol oral glucocorticoid taper to a low dose of ≤2.5 mg per day, with 83.1% and 80.4% of patients in the voclosporin and control groups receiving this dose at Week 16, 83.2% and 85.0% receiving it at 6 months, and 75.8% and 73.9% receiving it at one year, respectively (Supplementary Table 2, available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.25007). Exposure to MMF was similar, with mean ± SD daily doses of 1.84 ± 0.41 and 1.93 ± 0.38 gm per day in the voclosporin and control arms, respectively; a total of 18 (7.0%) and 29 (11.2%) patients in the voclosporin and control groups received mean daily doses of MMF of ≥2 gm.

Efficacy. A significantly higher proportion of patients in the voclosporin group achieved a CRR at one year (117 [43.7%] vs. 62 [23.3%]; odds ratio [OR] 2.76; 95% confidence interval [95% CI] 1.88, 4.05; $P < 0.0001$). Voclosporin treatment was also associated with a significantly higher CRR rate at six months (85 [31.7%] vs. 54 [20.3%]; OR 2.01; 95% CI 1.34, 3.01; $P = 0.0008$; Supplementary Figure 1, available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.25007. CRR rates

Table 1. Demographic and baseline patient disease characteristics*

Characteristic	Voclosporin (n = 268)	Control (n = 266)
Age, median (min, max), years	30 (18, 66)	32 (18, 72)
Sex, female	237 (88.4)	225 (84.6)
Weight, mean ± SD kg	65.3 ± 16.9	66.0 ± 16.1
Race		
White	98 (36.6)	103 (38.7)
Asian, Indian Subcontinent	22 (8.2)	18 (6.8)
Asian, other	83 (31.0)	74 (27.8)
Black	29 (10.8)	24 (9.0)
Other†	36 (13.4)	47 (17.7)
Ethnicity		
Hispanic or Latino	66 (24.6)	72 (27.1)
Not Hispanic or Latino	202 (75.4)	193 (72.6)
Unknown	0	1 (<1)
Region		
Asia: low GDP‡	61 (22.8)	47 (17.7)
Asia: high GDP§	43 (16.0)	40 (15.0)
Europe and South Africa	77 (28.7)	86 (32.3)
North and Latin America	87 (32.5)	93 (35.0)
Time since LN diagnosis, mean ± SD years	4.7 ± 5.1	4.5 ± 4.6
Median (IQR)	2.2 (1.3, 6.6)	2.2 (1.3, 6.8)
Time since SLE diagnosis, mean ± SD years	6.5 ± 6.2	6.4 ± 5.7
Biopsy class		
Class III	32 (11.9)	47 (17.6)
Class IV	135 (50.4)	118 (44.4)
Class V	37 (13.8)	38 (14.3)
Mixed class V and III or IV	64 (23.9)	63 (23.7)
Biopsy within 6 months prior to screening		
Yes	250 (93.3)	245 (92.1)
No	18 (6.7)	21 (7.9)
eGFR¶		
Corrected eGFR, mean ± SD ml/minute/1.73 m^2	79.0 ± 15.4	79.1 ± 15.9
Raw eGFR, mean ± SD ml/minute/1.73 m^2	93.2 ± 29.7	93.6 ± 28.6
Raw eGFR ≥60 ml/minute/1.73 m^2	226 (84.6)	225 (84.4)
UPCR, mean ± SD mg/mg	4.5 ± 3.3	4.1 ± 2.8
Complement 3, mean ± SD mg/dl	84.2 ± 35.8	88.1 ± 36.8
Complement 4, mean ± SD mg/dl	17.5 ± 13.3	16.8 ± 9.4
Anti-dsDNA, mean ± SD IU/ml	94.8 ± 114.2	90.3 ± 111.2
ACE inhibitor/ARB use	162 (60.7)	173 (65.0)
Hydroxychloroquine use#	145 (54.3)	153 (57.5)

* Values are number (percentage) unless otherwise indicated. ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; dsDNA = double-stranded DNA; eGFR = estimated glomerular filtration rate; GDP = gross domestic product; IQR = interquartile range; LN = lupus nephritis; SLE = systemic lupus erythematosus; UPCR = urine protein creatinine ratio.
† Other races include American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and other or mixed races except mixed Black race.
‡ Asia Low GDP includes Bangladesh, Philippines, Sri Lanka, and Vietnam. The threshold for "Low GDP" is approximately USD $5,000 per capita.
§ Asia High GDP includes Hong Kong, Japan, Korea, Malaysia, Taiwan, Thailand.
¶ Data missing for one patient in the voclosporin group.
# Includes all hydroxychloroquine and chloroquine derivatives used between Day −30 to Day −1.

were numerically greater in voclosporin-treated patients across all ages, races, regions, ethnicities, biopsy classes, and eGFR and UPCR levels at baseline (Figure 1). This includes patients with baseline UPCR of ≥2 gm, where 41.0% of voclosporin-treated patients achieved this end point, compared with 21.9% of control-treated patients (OR 2.48; 95% CI 1.62, 3.78; $P < 0.0001$). Further, the individual components of CRR were achieved more often in the voclosporin group, with significantly more patients achieving the UPCR less than or equal to 0.5 mg/mg component (Supplementary Table 3, available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.25007).

A significantly higher proportion of the voclosporin group achieved a PRR at one year (186 [69.4%] vs. 134 [50.6%]; OR 2.26; 95% CI 1.58, 3.23; $P < 0.0001$) and at six months (188 [70.1%] vs. 132 [49.8%]; OR 2.42; 95% CI 1.68, 3.48; $P < 0.0001$). A greater than or equal to 50% reduction in UPCR from baseline at any time was achieved by 93.7% of patients in the voclosporin group and 75.2% of patients in the control group. Overall, the median time to a 50% reduction in UPCR were 29 days (range 29–31) and 58 days (range 57–85), respectively (hazard ratio [HR] 1.96; 95% CI: 1.61, 2.38; $P < 0.0001$); the difference between treatment groups was apparent within the first month and sustained at one year (Figure 2). Similarly, voclosporin led to significantly shorter median times for this end point in patients with class III and class IV disease compared to their respective control groups: 25 vs. 84 days (class III: $P = 0.0146$) and 29 vs. 57 days (class IV: $P < 0.0001$; Supplementary Table 1), respectively. Voclosporin was also associated with a shorter median time for this end point in class V patients, but the difference was not statistically significant.

More patients in the voclosporin group achieved a UPCR less than or equal to 0.5 mg/mg at any time during the study (173 [64.6%] vs. 111 [41.7%]). Patients treated with voclosporin achieved this threshold faster than control-treated patients regardless of biopsy class (Supplementary Table 1, available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25007). Overall, the median time to reach this threshold was 169 days (range 139–212) for the voclosporin group; a median time was not reached for the control group as the majority of patients did not achieve UPCR of ≤0.5 mg/mg during the study (HR 2.13; 95% CI: 1.67, 2.72; $P < 0.0001$). The difference between groups in time to UPCR ≤0.5 mg/mg was apparent within the first month and sustained at one year. Median times to UPCR ≤0.5 mg/mg for class III and class IV disease were significantly shorter with voclosporin treatment compared to control: 142 vs. 372 days (class III: $P = 0.0407$) and 142 vs. not determinable days (class IV: $P < 0.0001$). Voclosporin-treated class V patients achieved this end point earlier than control-treated patients as well, but the difference was not statistically significant.

Mean changes in UPCR from baseline were greater for the voclosporin group than the control group and were statistically significant at all timepoints including at one year (–3.3 vs. –2.4 mg/mg, respectively; MMRM difference between groups, –1.1 [95% CI: –1.5, –0.7; $P < 0.0001$]).

Mean C3 and C4 values were comparable at screening (C3: 84.2 and 88.1 mg/dl; C4: 17.5 and 16.8 mg/dl in the

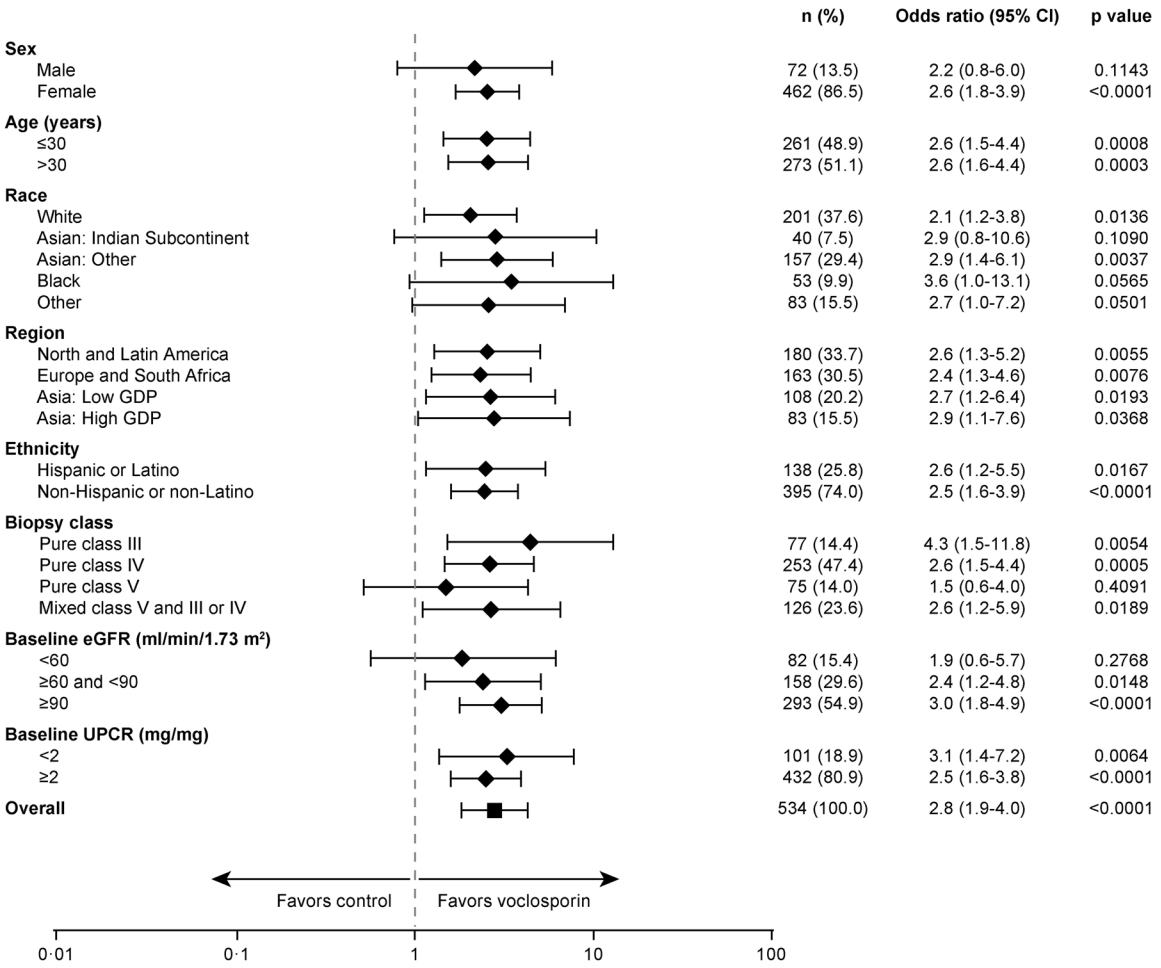

Figure 1. Analysis of complete renal response at one year by demographic and disease subgroups. Pooled analysis of complete renal response at 1 year includes integrated data from the voclosporin 23.7 mg BID and control treatment groups at 48 weeks for Aurinia Urinary Protein Reduction in Active Lupus with Voclosporin (AURA-LV) and at 52 weeks for Aurinia Renal Response in Active Lupus With Voclosporin (AURORA 1). Analysis uses a logistic regression model with covariates for study, treatment group, subgroup, and treatment by subgroup interaction. Asia: Low gross domestic product (GDP) includes Bangladesh, Philippines, Sri Lanka, and Vietnam. The threshold for 'Low GDP' is approximately USD $5,000 per capita. Asia: High GDP includes Hong Kong, Japan, Korea, Malaysia, Taiwan, Thailand. eGFR = estimated glomerular filtration rate; UPCR = urine protein creatinine ratio.

voclosporin and control groups, respectively) and at one year (C3: 99.7 and 99.6 mg/dl; C4: 20.5 and 19.3 mg/dl in the voclosporin and control groups, respectively). Mean anti-dsDNA levels were comparable at screening (94.8 IU/ml and 90.3 IU/ml in the voclosporin and control groups, respectively); in the MMRM analysis, significantly larger decreases in mean anti-dsDNA at one year were observed in the voclosporin group than in the control group (–36.0 IU/ml vs. –22.0 IU/ml; 95% CI: –25.2, –2.8; $P = 0.0144$).

Safety. The incidence of AEs was similar, with 244 (91.4%) and 232 (87.2%) patients in the voclosporin and control groups, respectively, experiencing an AE. AEs were the most common reason for treatment discontinuation, with similar rates in both the voclosporin (38 [14.2%]) and control (33 [12.4%]) groups (Table 2). The majority of AEs were mild or moderate in severity (191 [71.5%] and 195 [73.3%] in the voclosporin and control groups, respectively).

AEs in the Medical Dictionary for Regulatory Activities (MedDRA) System Order Class of "Infections and Infestations" were the most commonly reported (166 [62.2%] in the voclosporin group and 146 [54.9%] in the control group; Supplementary Table 4) and were deemed to be treatment related in 40 (15%) and 30 (11.3%) patients, respectively. The most commonly reported treatment-related infections in the voclosporin and control groups were herpes zoster (10 [3.7%] and four [1.5%]), urinary tract infection (seven [2.6%] and two [0.8%]), and upper respiratory tract infection (seven [2.6%] in both groups).

Four (1.5%) patients, all in the voclosporin group, had events identified using the "Malignancies" Structured MedDRA Query, including single cases of stage 0 cervical carcinoma (carcinoma

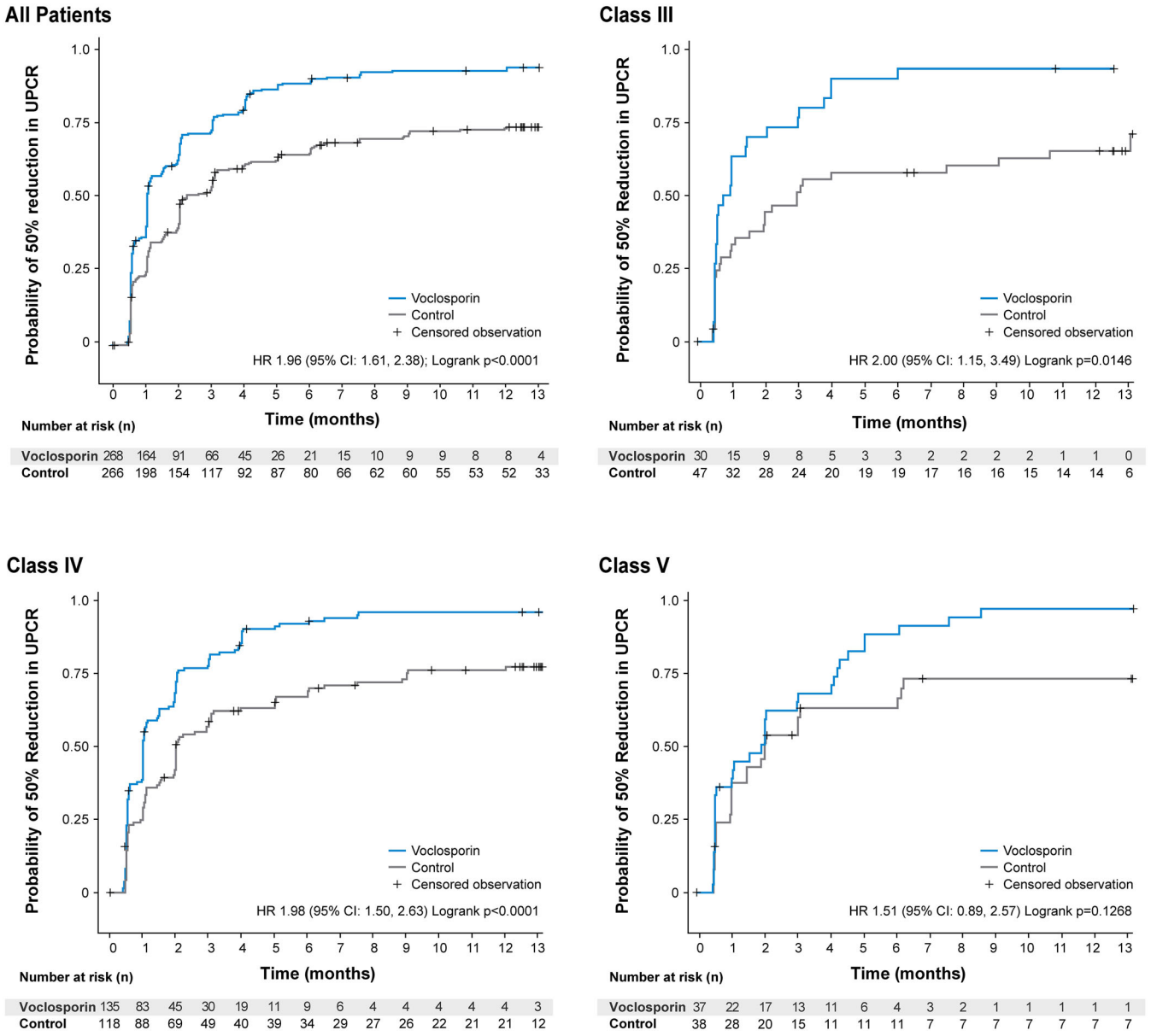

Figure 2. Time to 50% reduction in urine protein creatinine ratio (UPCR) from baseline in all Patients and by biopsy class. Kaplan-Meier analysis of time to 50% reduction in UPCR from baseline includes integrated data from the voclosporin 23.7 mg BID and control treatment groups treated up to 48 weeks in AURA-LV and up to 52 weeks in AURORA 1. Two patients were reclassified post hoc as class III. These patients are included in the overall analysis but excluded from biopsy class III subgroup analyses. AURA-LV = Aurinia Urinary Protein Reduction in Active Lupus with Voclosporin; AURORA 1 = Aurinia Renal Response in Active Lupus With Voclosporin; HR = hazard ratio; 95% CI = 95% confidence interval.

in situ), skin neoplasm (pigmented tumor on toe), pyoderma gangrenosum (not considered malignant), and breast tumor excision (fibroadenoma). There was one pregnancy in the voclosporin group reported during the study that ended by induced abortion.

Overall, there were 17 (3.0%) deaths (all previously reported) (18,19). The incidence of mortality was similar between voclosporin (11 [4.1%]) and control-treated (six [2.3%]) patients. All events of mortality were considered multifactorial and unrelated to study treatment per study investigators. A higher incidence of mortality was observed in AURA-LV (10 [11.2%] in the voclosporin group and 1 [1.1%] in the control group) than in AURORA 1 (one [0.6%] and four [2.8%], respectively). The majority of deaths in AURA-LV (82%) occurred in patients from a few sites in Bangladesh, Sri Lanka, and the Philippines who had more severe disease characteristics at baseline. A higher proportion of patients from these countries were enrolled in the voclosporin arm than in the control arm; these trial sites were not included in AURORA 1.

Mean corrected eGFR values remained within normal range at all timepoints in both groups (Supplementary Figure 2, available on the *Arthritis Care & Research* website at

Table 2. Summary of adverse events*

Event	Voclosporin (n = 267)	Control (n = 266)
AE	244 (91.4)	232 (87.2)
SAE	61 (22.8)	50 (18.8)
SAE of infections and infestations	27 (10.1)	27 (10.2)
Treatment-related SAE	12 (4.5)	9 (3.4)
AE leading to study drug discontinuation	36 (13.5)	35 (13.2)
Death	11 (4.1)	6 (2.3)
Treatment-related AE leading to death	0	0
AEs of interest		
Glomerular filtration rate decreased	70 (26.2)	25 (9.4)
Hypertension	51 (19.1)	23 (8.6)
Anemia	33 (12.4)	16 (6.0)
Alopecia	17 (6.4)	7 (2.6)
Tremor	9 (3.4)	2 (0.8)
Seizure/convulsion	3 (1.1)	0
Hyperglycemia	2 (0.7)	4 (1.5)
QTc prolongation	2 (0.8)	2 (0.8)
Posterior reversible encephalopathy	1 (0.4)	0
Pure red cell aplasia	0	0

* Values are number (percentage). Includes adverse events (AEs) that occurred on or after the day of the first dose of study drug including up to 30 days after the last dose and all events of death reported during study follow-up. AEs occurring up to the end of the last day in AURORA 1 were included for patients who transitioned into the AURORA 2 extension study. AEs were aggregated by system organ class and preferred term and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. AURORA = Aurinia Renal Response in Active Lupus With Voclosporin; SAE = serious adverse event.

https://onlinelibrary.wiley.com/doi/10.1002/acr.25007). Due to the hemodynamic effect of CNIs, there was an expected, early decrease in mean ± SD corrected eGFR in the voclosporin arm of –3.4 ± 13.7 ml/minute/1.73 m^2 at Week 4, after which eGFR remained stable. GFR decreased was the most frequently reported AE by Preferred Term (PT), occurring in 70 (26.2%) and 25 (9.4%) patients in the voclosporin and control groups, respectively (Table 2). Severe events were reported in seven (2.6%) and five (1.9%) patients, respectively. Dose modifications due to GFR decrease occurred in 63 (23.6%) patients in the voclosporin group and 18 (6.8%) patients in the control group. Ten (3.7%) and five (1.9%) patients, respectively, discontinued study treatment due to GFR decrease. Of the 10 patients in the voclosporin arm, four saw a recovery in eGFR within three months; in the remaining six patients, the event was ongoing as of last follow-up (three continued until study completion, one withdrew prior to study completion, and two died secondary to other AEs). Of the five control-treated patients, one saw recovery in eGFR within three months and one within six months; the event was ongoing in the remaining three patients as of last follow-up (two continued until study completion, and one withdrew prior to study completion).

The second most frequent AE by PT was hypertension, reported in 51 (19.1%) and 23 (8.6%) patients in the voclosporin and control groups, respectively. In voclosporin-treated patients, hypertension was most frequently reported over the first four weeks and then progressively decreased over the analysis period. Five (1.9%) voclosporin-treated patients had serious events of hypertension; an additional patient had a serious event of hypertensive crisis. All six patients with serious events saw resolution of their event without sequelae. Four completed the study on therapy; the remaining two discontinued voclosporin for reasons unrelated to hypertension. One serious event of hypertension was reported in a control-treated patient (0.4%), and hypertensive crisis was reported in two (0.8%); no patients had study treatment discontinued due to hypertension. Overall, increases in mean systolic and diastolic blood pressure were transient, and mean values were within normal ranges throughout the studies (Supplementary Figure 3, available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.25007).

Two patients in each group had QTcF prolongation greater than 60 msec compared to baseline; no patient recorded a QT interval greater than 500 msec. Both patients in the voclosporin group and one patient in the control group were receiving concomitant hydroxychloroquine or chloroquine at the time of event. The study drug was discontinued in one voclosporin-treated patient due to the event and in a second due to worsening kidney function. No patient reported symptoms or required treatment due to the abnormal ECG findings; there were no reports of torsades de pointes. Additional AEs of interest are outlined in Table 2.

Mean glucose and glycated hemoglobin (HbA1c) levels were stable over the analysis periods in both groups, with no meaningful changes from baseline. Overall, two (0.7%) and four (1.5%) patients in the voclosporin and control groups, respectively, experienced AEs of hyperglycemia.

Lipid profiles improved in both groups during treatment, with significantly greater improvements in total and low-density lipoprotein (LDL) cholesterol in patients receiving voclosporin. At one year, the mean ± SD reduction in total cholesterol was –82.6 ± 93.06 mg/dl in the voclosporin group and –61.6 ± 92.18 mg/dl in the control group ($P = 0.0062$). Similarly, mean ± SD reductions were seen at one year in LDL cholesterol levels (–57.4 ± 78.51 mg/dl and –44.1 ± 77.87 mg/dl, respectively [$P = 0.0234$]) and in triglyceride levels (–74.1 ± 110.62 mg/dl and –48.4 ± 117.08 mg/dl, respectively [$P = 0.0768$], Supplementary Table 5). During the studies, lipid-modifying agents (e.g., statins, fibrates, etc.) were initiated in 36 (13.5%) and 45 (16.9%) patients in the voclosporin and control groups, respectively.

Mean levels of potassium and magnesium remained within normal ranges for both groups at all timepoints with no patients displaying symptoms of or requiring treatment for an electrolyte disturbance (Supplementary Figures 4 and 5, available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.

com/doi/10.1002/acr.25007). Mean leukocyte, lymphocyte, and neutrophil counts remained within normal ranges at all timepoints in both groups.

DISCUSSION

This integrated analysis of 534 patients with LN demonstrated significantly higher CRR rates at six months and one year when voclosporin was added to MMF and glucocorticoids. Consistent with other recent studies demonstrating CRR rates of 20% to 30% after one year with standard of care treatment, the control arm in this analysis had a CRR rate of 23.3%. Addition of voclosporin increased the rate of response more than 20%, a notable improvement, consistent with other successful clinical trials in LN and strong evidence of the treatment benefit of voclosporin (20). Further, the reduction in proteinuria seen with voclosporin was achieved early, within the first 6 months of treatment, and maintained throughout the analysis period. These rapid reductions in proteinuria are a promising finding shown to be highly predictive of positive long-term renal outcomes (6,8,11,21).

As this analysis combined the diverse populations enrolled in two individual studies, it allowed for further investigation into the impact of voclosporin across races, ethnicities, and geographical regions, all of which have been shown to affect treatment response in LN (22–24). In contrast to previous studies of CNI treatment in LN dominated by Asian patient cohorts, the voclosporin studies are the first to demonstrate significantly higher CRR rates achieved with a CNI across a wider range of races and ethnicities (23–26). Also, this analysis has further demonstrated the efficacy of voclosporin across biopsy classes, with voclosporin not only associated with a higher likelihood of CRR in all classes but also with earlier reductions in proteinuria. Voclosporin has also been recently shown to be effective in patients with newly diagnosed LN and patients with severe disease, with both populations achieving significantly greater rates of CRR with voclosporin than MMF and glucocorticoids alone (27,28). Taken together, these data demonstrate the clinical benefit of voclosporin, making it a viable treatment option for certain patient populations that have traditionally been considered more difficult-to-treat.

Chronic exposure to glucocorticoids increases the risk of serious infection and organ toxicity, and minimizing exposure in the treatment of LN is essential (29). To that end, both trials in this analysis incorporated a glucocorticoid-tapering protocol consistent with the 2019 update of the EULAR and European Renal Association–European Dialysis and Transplant Association treatment recommendations for LN as well as the 2021 update of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, as both recommend tapering oral prednisone to less than or equal to 7.5 mg per day by 3 to 6 months (6,30). More than 80% of patients in both groups of the current analysis were receiving a prednisone or equivalent dose of less than or equal to 2.5 mg per day by Week 16, with approximately 75% on less than or equal to 2.5 mg per day at 1 year. This indicates that most patients who achieved a CRR did so in the absence of traditional high-dose glucocorticoids. These data demonstrate that an immunosuppression regimen with voclosporin is highly effective in LN despite significant reductions in cumulative glucocorticoid dose and add to a growing body of evidence suggesting traditional high-dose glucocorticoids are not necessary to achieve remission (12,31–33).

This analysis also allows for further characterization of the voclosporin safety profile. No new or unexpected safety signals were observed, and AEs remained as expected for a population with LN receiving immunosuppressive treatment.

Calcineurin inhibition results in a hemodynamically mediated decrease in eGFR occurring through dose-dependent vasoconstriction within the nephron (1,17). In the current analysis, the voclosporin group had an anticipated reduction in mean corrected eGFR at Week 4, after which mean levels remained stable through the one-year treatment period. These hemodynamic changes were managed by a predefined eGFR-based dosing protocol. The linear pharmacokinetic profile and the concentration-dependent calcineurin inhibition of voclosporin allow for the use of this pharmacodynamic-based approach to dosing, in which the dose is adjusted in response to decreases in eGFR, in contrast to the need for therapeutic drug monitoring associated with traditional CNIs.

Besides hypertension, there was no increased signal for classically CNI-attributed complications, such as diabetes, dyslipidemia, hyperkalemia, or hypomagnesemia, observed in the voclosporin-treated cohort (17,34). Instead, lipid profiles improved in voclosporin-treated patients, and mean blood pressure, glucose, and electrolyte levels were stable and similar between the groups.

A limitation of this integrated analysis was that study data were of maximal one-year duration. The AURORA 2 continuation study was recently completed and included 216 patients who transitioned from AURORA 1 on the same randomized treatment. With up to three years total duration, AURORA 2 provides longer-term safety and efficacy data on the combination of voclosporin with MMF and glucocorticoids and further insight into the utility of this therapy in LN.

Of note, patients in AURORA 1 were allowed to enter the study based on a renal biopsy performed within two years prior to enrollment, and disease activity may have changed between the biopsy and study start. However, nearly 90% of patients enrolled in AURORA 1 and all patients in AURA-LV had a biopsy less than six months prior to enrollment, resulting in only 6.7% and 7.9% of patients in the voclosporin and control groups, respectively, with biopsies more than six months prior to enrollment. Further, biopsy results more than six months old had to be accompanied by at least a doubling in UPCR within the six

months prior to screening to a minimum of greater than or equal to 1.5 mg/mg (≥2 mg/mg for class V disease).

There are a few characteristics of the population under study that may differ from other study populations in LN. Firstly, patients in this analysis had a longer mean duration since LN diagnosis than that reported in other studies, which may be further indication of the diversity of patients enrolled in the voclosporin clinical program. Also, given hydroxychloroquine is recommended as first-line therapy for LN, the percentage of patients on antimalarials at screening was lower than expected, between 55% and 60% in both groups. As there was no requirement to have been on hydroxychloroquine prior to study start nor to initiate treatment during the study, the proportion of patients on this therapy at screening is likely a reflection of real-world treatment patterns.

Finally, despite pooling data from AURA-LV and AURORA 1, the number of patients with historically more difficult-to-treat disease, including Black patients and those with class V disease, remained quite low. While consistent with other LN studies, the low numbers complicate the interpretation of the results for these populations. Similarly, patients with a baseline eGFR under 45 mL/min/1.73 m^2, a population that may require more aggressive treatment to avoid renal replacement therapy, were excluded from participating; the efficacy of voclosporin in this group is not yet known.

The data from this analysis confirm the efficacy of voclosporin reported previously, with no new or unexpected safety signals observed in this larger patient population (1). The confirmation of efficacy in a diverse population provides further support for the use of voclosporin as a first-line, oral therapy 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 submitted for publication. All authors had full access to all of the study data. Lisk, Randhawa, Gluck, Solomons, and Huizinga take responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Arriens, Teng, Ginzler, Parikh, Askanase, Saxena, Gibson, Caster, Atsumi, Lisk, Randhawa, Gluck, Solomons, Huizinga.

ROLE OF THE STUDY SPONSOR

Aurinia Pharmaceuticals Inc. had a role 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 Inc.

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