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# 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

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**Calcineurin inhibitors added to standard-of-care induction therapy for lupus nephritis (LN) may increase complete renal remission (CRR) rates. The AURA-LV study tested the novel calcineurin inhibitor voclosporin for efficacy and safety in active LN. AURA-LV was a Phase 2, multicenter, randomized, double-blind, placebo-controlled trial of two doses of voclosporin (23.7 mg or 39.5 mg, each twice daily) versus placebo in combination with mycophenolate mofetil (2 g/d) and rapidly tapered low-dose oral corticosteroids for induction of remission in LN. The primary endpoint was CRR at 24 weeks; the secondary endpoint was CRR at 48 weeks. Two hundred sixty-five subjects from 79 centers in 20 countries were recruited and randomized to treatment for 48 weeks. CRR at week 24 was achieved by 29 (32.6%) subjects in the low-dose voclosporin group, 24 (27.3%) subjects in the high-dose voclosporin group, and 17 (19.3%) subjects in the placebo group (OR=2.03 for low-dose voclosporin versus placebo). The significantly greater CRR rate in the low-dose voclosporin group persisted at 48 weeks, and CRRs were also significantly more common in the high-dose voclosporin group compared to placebo at 48 weeks. There were more serious adverse events in both voclosporin groups, and more deaths in the low-dose group compared to placebo and high-dose voclosporin groups (11.2%, 1.1%, and 2.3%, respectively). These results suggest that the addition of low-dose voclosporin to mycophenolate mofetil and corticosteroids for induction therapy of active LN results in a superior renal response compared to mycophenolate mofetil and corticosteroids alone, but higher rates of adverse events including death were observed.**

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**KEYWORDS:** calcineurin inhibitors; glomerulonephritis; kidney biopsy; proteinuria; systemic lupus erythematosus

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Lupus nephritis (LN) is the most common serious manifestation of systemic lupus erythematosus (SLE) and can cause permanent and irreversible damage to the kidney. In persons with LN the main goal of therapy is to prevent the development of chronic kidney disease, end-stage kidney disease, and death.<sup>1</sup> Because these outcomes accrue slowly, short-term complete and partial renal remissions are used to assess the efficacy of standard-of-care and novel LN therapies.<sup>2,3</sup> However, after 6 to 12 months of treatment, only 10% to 40% of patients achieve a complete renal remission (CRR) with standard-of-care therapy.<sup>4</sup> These results underscore the need for more effective LN therapies.

Calcineurin inhibitors (CNIs) are used to prevent allograft rejection in persons undergoing kidney transplantation by blocking T-cell activation.<sup>5–7</sup> By attenuating T-cell responses, a CNI combined with a general immunosuppressive agent and an antiinflammatory drug could increase the CRR rate of patients with LN. This concept formed the basis of a multi-target regimen that has undergone considerable investigation in China. In the largest randomized controlled Chinese trial, the CNI tacrolimus was used in combination with mycophenolate mofetil (MMF) and corticosteroids and was found to induce a significantly higher number of CRRs at 6 months compared with standard of care with cyclophosphamide plus corticosteroids.<sup>8</sup> To date, the combination of MMF and a CNI has not been applied to an ethnically diverse LN population.

Voclosporin (VCS) is a next-generation CNI developed using a pharmacodynamic approach for a variety of systemic, pulmonary, and dermatologic autoimmune indications. VCS is structurally similar to cyclosporine A (CsA) except for a

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modification of a functional group on amino acid-1 of the molecule.<sup>9</sup> This alteration changes how VCS binds calcineurin, leading to an increase in potency up to 4-fold when compared with CsA. This modification also changes the metabolic profile of VCS by shifting metabolism away from amino acid-1, the major site of metabolism for CsA. The altered metabolic profile leads to a faster elimination of metabolites, resulting in lower metabolite exposure compared with CsA. The combination of increased potency and decreased metabolite exposure for VCS results in more pharmacokinetic and pharmacodynamic predictability than does CsA, and therefore drug level monitoring is not required.<sup>10</sup> In nonclinical and clinical studies, VCS demonstrated advantages compared with CsA and tacrolimus with respect to dosing and tolerability.

To test the efficacy and safety of a CNI-based approach to LN remission induction in a global cohort, the AURA-LV study compared VCS with placebo on background therapy of MMF and low- to medium-dose corticosteroids with a rapid taper in a randomized, controlled, prospective, double-blind phase 2 trial. The study investigated whether 2 doses of VCS added to background therapy in persons with active LN were more effective in inducing CRR than the background therapy alone after 24 weeks. Secondary objectives were to assess the safety, tolerability, and efficacy of VCS compared with placebo after 48 weeks of treatment.

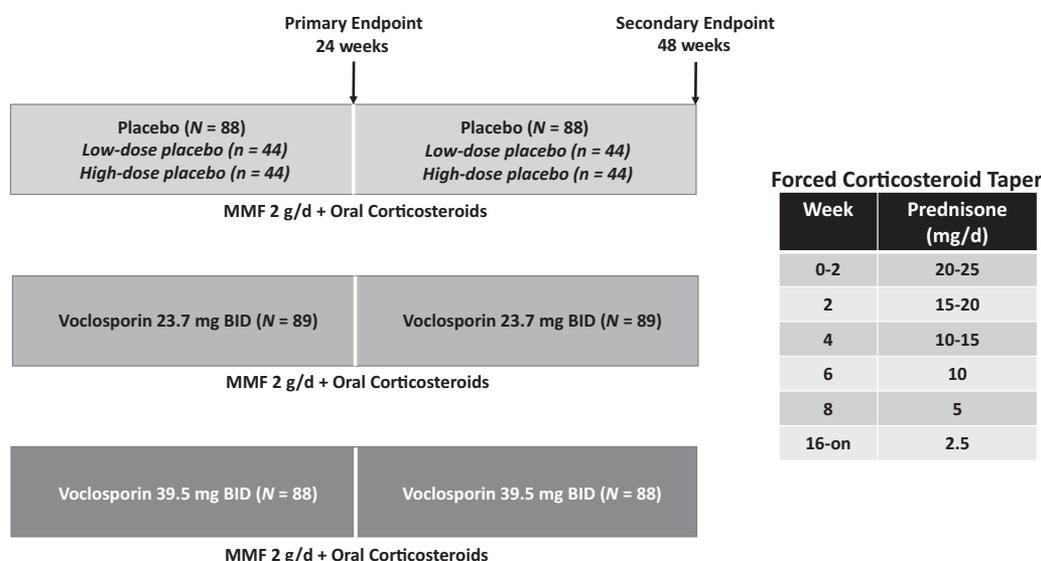
**RESULTS**

The AURA-LV trial was designed to test the efficacy and safety of adding VCS to background MMF plus corticosteroids for the initial treatment of LN (Figure 1). The trial randomized 265 subjects from 79 centers in 20 countries across the Americas, Europe, and Asia. In this intent-to-treat population, 88 subjects were randomly assigned to placebo (44 to low-dose placebo and 44 to high-dose placebo), 89 were

assigned to low-dose VCS (23.7 mg twice a day), and 88 were assigned to high-dose VCS (39.5 mg twice a day). Subject demographics and key baseline characteristics are provided in Table 1. Prior immunosuppressive drugs used and concomitant medications at trial entry are listed in Supplementary Tables S1 and S2. In the placebo group, 70 patients (79.5%) completed 48 weeks of treatment compared with 73 patients (82.0%) and 80 patients (90.9%) in the low- and high-dose VCS groups, respectively. Numeric differences existed between groups (Table 1), but these differences did not appear to relate to outcomes. For example, the high-dose VCS group included fewer men, which should have favored response, but it did not appear to do so. Similarly, the low-dose VCS arm had fewer white patients, which should have favored nonresponse, but it did not appear to do so. Patient flow in the trial is shown in Supplementary Figure S1.

**Primary endpoint**

The CRR rate was significantly higher with low-dose VCS (23.7 mg twice a day) than with placebo at week 24 (Figure 2). CRR was achieved by 32.6% of subjects in the low-dose group (odds ratio [OR] = 2.03; 95% confidence interval [CI]: 1.01–4.05; *P* = 0.046) and by 27.3% in the high-dose VCS group (OR = 1.59; 95% CI: 0.78–3.27; *P* = 0.204) compared with 19.3% in the placebo group (Figure 2). Both low-dose and high-dose VCS were superior to placebo with respect to CRR at week 48 (Figure 2). CRR was achieved by 49.4% of subjects in the low-dose VCS group (OR = 3.21; 95% CI: 1.68–6.13; *P* < 0.001) and 39.8% of subjects in the high-dose VCS group (OR = 2.10; 95% CI: 1.09–4.02; *P* = 0.026), compared with 23.9% in the placebo group. Using Kaplan-Meier analysis, CRRs were achieved more rapidly (*P* < 0.001) in both VCS groups compared with placebo (data not shown). The median time to CRR was 19.7 weeks for the low-dose VCS group and 23.4 weeks for the high-dose VCS group. Median time to CRR



**Figure 1 | AURA trial design and corticosteroid tapering protocol.** BID, twice a day; MMF, mycophenolate mofetil.

**Table 1 | Baseline demographics and disease characteristics**

Variable	Placebo (N = 88)	Voclosporin low dose (N = 89)	Voclosporin high dose (N = 88)	Total (N = 265)
Age, yr				
Mean (SD)	33.1 (10.0)	31.4 (11.8)	30.6 (9.6)	31.7 (10.5)
Sex, n (%)				
Male	15 (17.0)	13 (14.6)	7 (8.0)	35 (13.2)
Female	73 (83.0)	76 (85.4)	81 (92.0)	230 (86.8)
Weight, kg				
Mean (SD)	65.0 (16.3)	62.5 (16.7)	66.3 (19.2)	64.6 (17.4)
Race, n (%)				
White	42 (47.7)	30 (33.7)	36 (40.9)	108 (40.8)
Black	5 (5.7)	3 (3.4)	6 (6.8)	14 (5.3)
Asian-Indian subcontinent <sup>a</sup>	18 (20.5)	22 (24.7)	20 (22.7)	60 (22.6)
Asian—other <sup>a</sup>	18 (20.5)	30 (33.7)	24 (27.3)	72 (27.2)
Other	5 (5.7)	4 (4.5)	2 (2.3)	11 (4.2)
Ethnicity, n (%)				
Hispanic	13 (14.8)	9 (10.1)	13 (14.8)	35 (13.2)
Non-Hispanic	75 (85.2)	80 (89.9)	75 (85.2)	230 (86.8)
Region, n (%)				
Americas <sup>b</sup>	19 (21.6)	12 (13.5)	20 (22.7)	51 (19.2)
Europe <sup>c</sup>	34 (38.6)	25 (28.1)	25 (28.4)	84 (31.7)
Asia <sup>a</sup>	35 (39.8)	50 (58.4)	43 (48.9)	130 (49.1)
Time since initial LN diagnosis, yr				
Mean (SD)	3.5 (4.0)	4.2 (5.1)	3.2 (4.4)	3.7 (4.5)
Biopsy class, n (%)				
Pure Class V	13 (14.8)	12 (13.5)	14 (15.9)	39 (14.7)
Class III/IV	59 (67.0)	56 (62.9)	63 (71.6)	178 (67.2)
Class III+V and IV+V	16 (18.2)	21 (23.6)	11 (12.5)	48 (18.1)
Baseline eGFR (ml/min per 1.73 m <sup>2</sup> )				
Mean (SD)	100.2 (27.1)	95.3 (28.4)	104.0 (27.3)	99.8 (27.7)
Baseline UPCR (mg/mg)				
N	87	89	88	264
Mean (SD)	4.43 (3.6)	5.16 (4.2)	4.48 (3.0)	4.69 (3.6)
MMF use at screening, n (%)				
Yes	32 (36.4)	31 (34.8)	29 (33.0)	92 (34.7)
No	56 (63.6)	58 (65.2)	59 (67.0)	173 (65.3)
MMF dose at screening (g/d)				
Mean (SD)	1.2 (0.5)	1.2 (0.4)	1.3 (0.5)	1.3 (0.5)

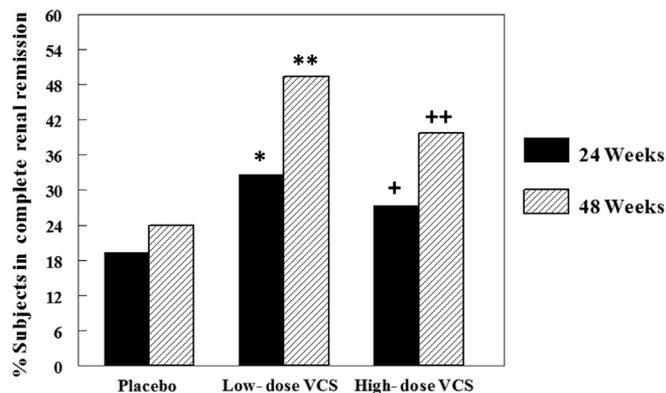
eGFR, estimated glomerular filtration rate; LN, lupus nephritis; MMF, mycophenolate mofetil; UPCR, urine protein to creatinine ratio.

<sup>a</sup>Bangladesh, Sri Lanka (Asian-Indian Subcontinent) + Hong Kong, Korea, Philippines, Singapore, Taiwan, Thailand (Asian—other).

<sup>b</sup>Ecuador, Guatemala, Mexico, USA.

<sup>c</sup>Belarus, Bulgaria, Georgia, Poland, Russia, Serbia, Spain, Ukraine.

could not be calculated for the placebo group because this group never reached 50% survival probability. Treatment with VCS also was associated with a statistically significant earlier time to partial remission (defined as a  $\geq 50\%$  decrease in



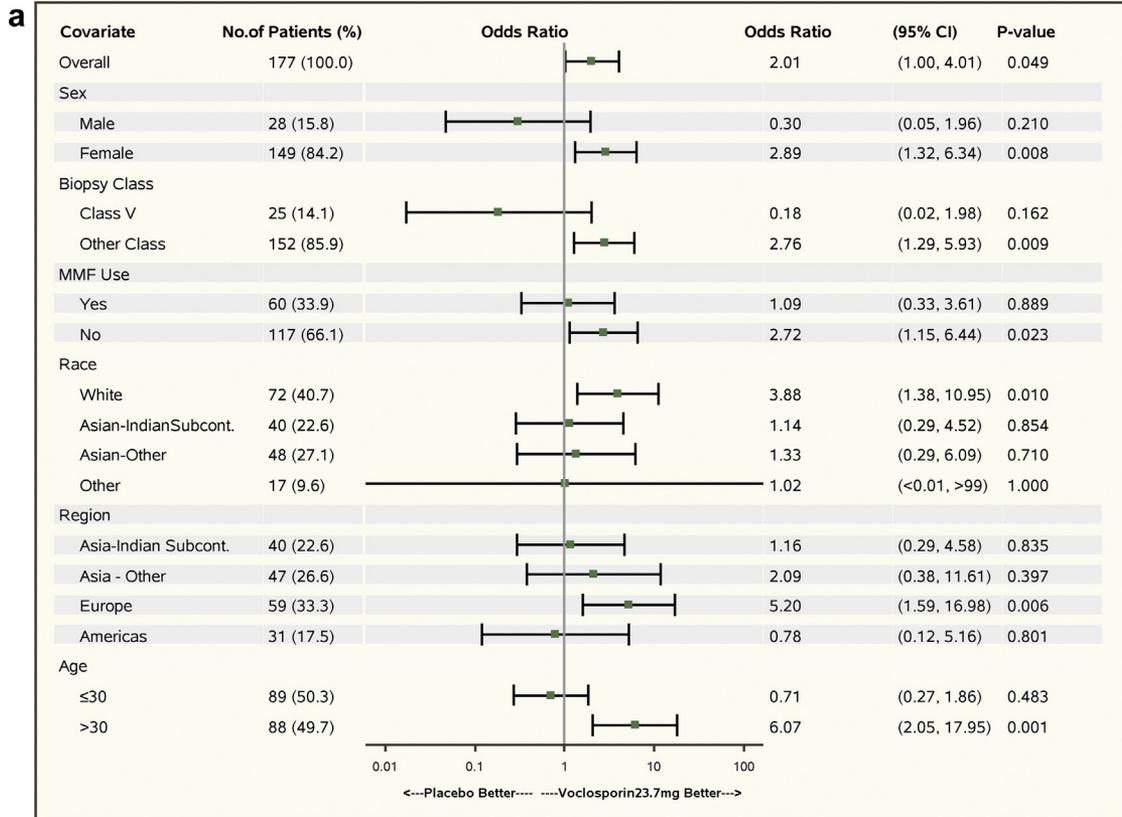
**Figure 2 | Complete renal remission at 24 and 48 weeks for the full analysis set.** VCS, voclosporin. \* $P = 0.046$ , \*\* $P < 0.001$ , + $P = 0.20$ , ++ $P = 0.026$  versus placebo.

urine protein to creatinine ratio [UPCR] from baseline in the absence of rescue medication, data not shown). Additionally, patients treated with VCS demonstrated a statistically significant decrease in UPCR and increase in serum albumin (Supplementary Figure S2). After withdrawal of VCS at week 48, a small increase in UPCR was noted in all groups by week 50, but the difference between the VCS and placebo groups remained statistically significant ( $P < 0.006$ ).

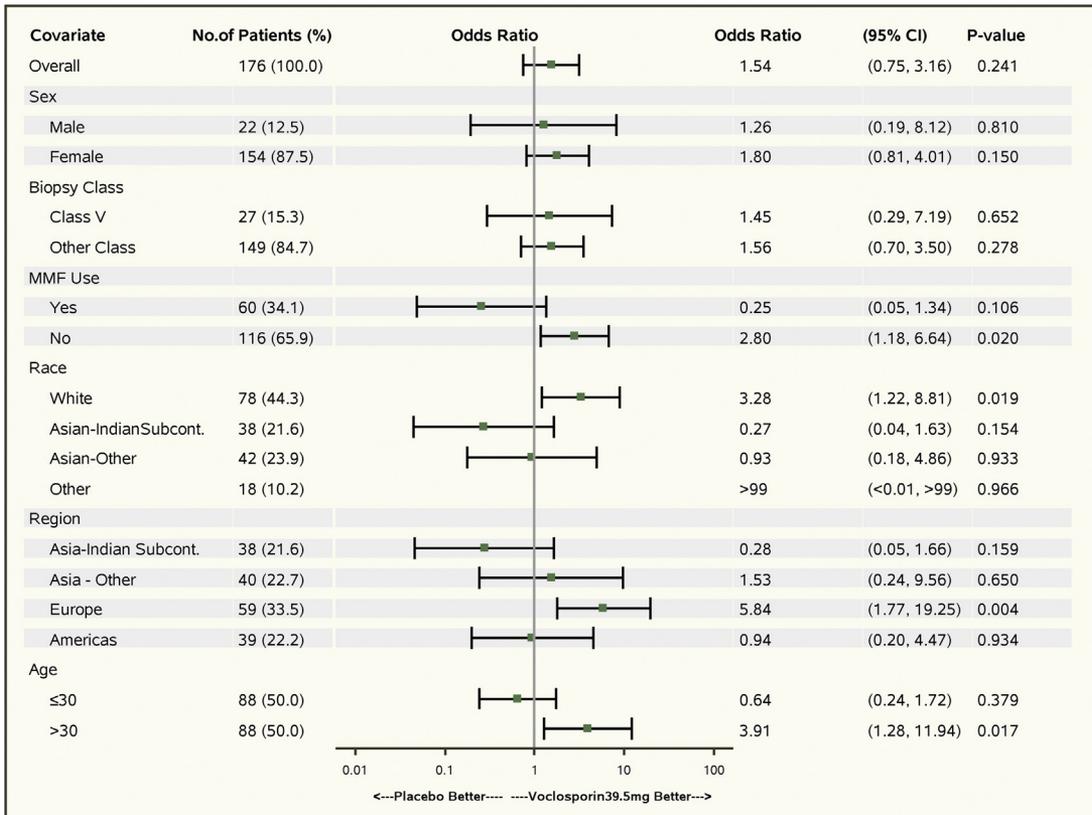
A treatment effect of VCS on CRR at weeks 24 and 48 was suggested but did not achieve statistical significance across the covariates of sex, MMF use at screening, race, region, and age (Figure 3). Interestingly, patients with a Class V component did not show a benefit with VCS treatment. Durability of remission was generally good, with all low-dose VCS subjects who were in remission at 24 weeks remaining so at 48 weeks (Figure 4).

Serologic indicators of SLE activity, including anti-dsDNA antibody and complement levels, improved over time in all of the treatment groups (Supplementary Figure S3), with a statistically significant improvement noted in anti-double-

Low-Dose Voclosporin Week 24

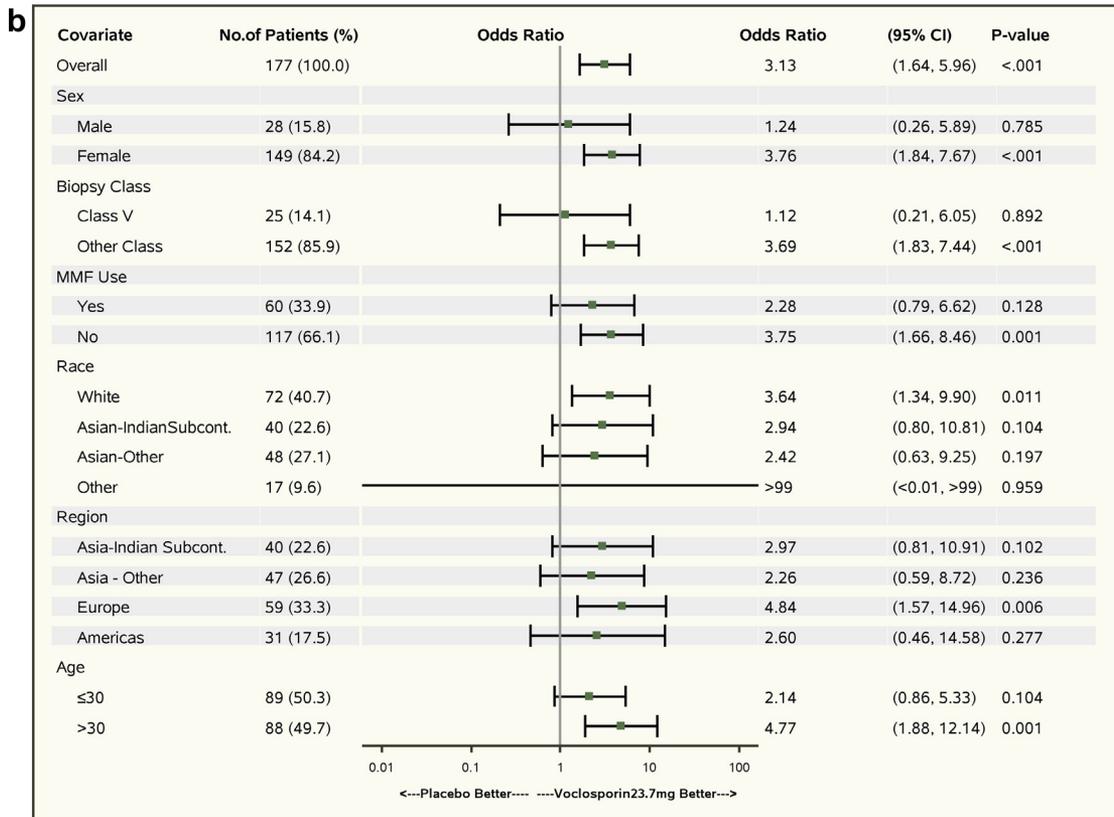


High-Dose Voclosporin Week 24

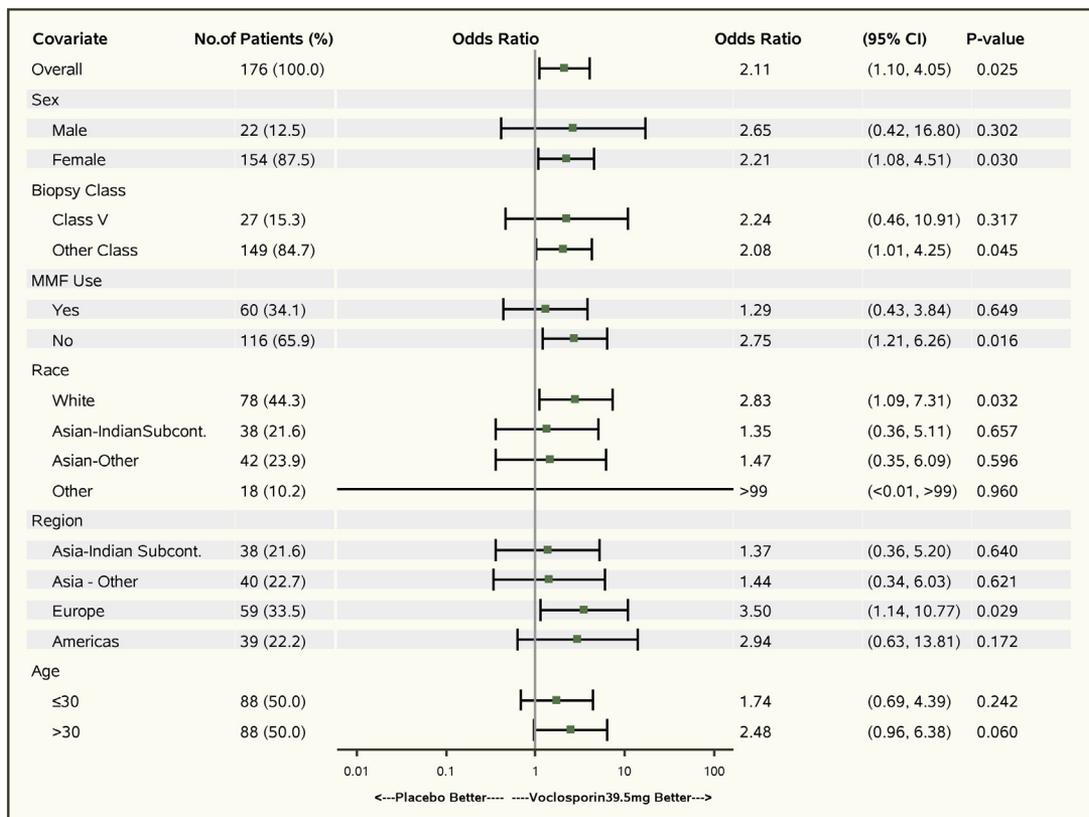


**Figure 3 | Covariate analysis.** Forest plots of complete renal remission at (a) 24 and (b) 48 weeks for the full analysis set are shown. These plots describe the odds ratios for voclosporin compared with placebo for several covariates of interest. All odds ratios and 95% confidence intervals

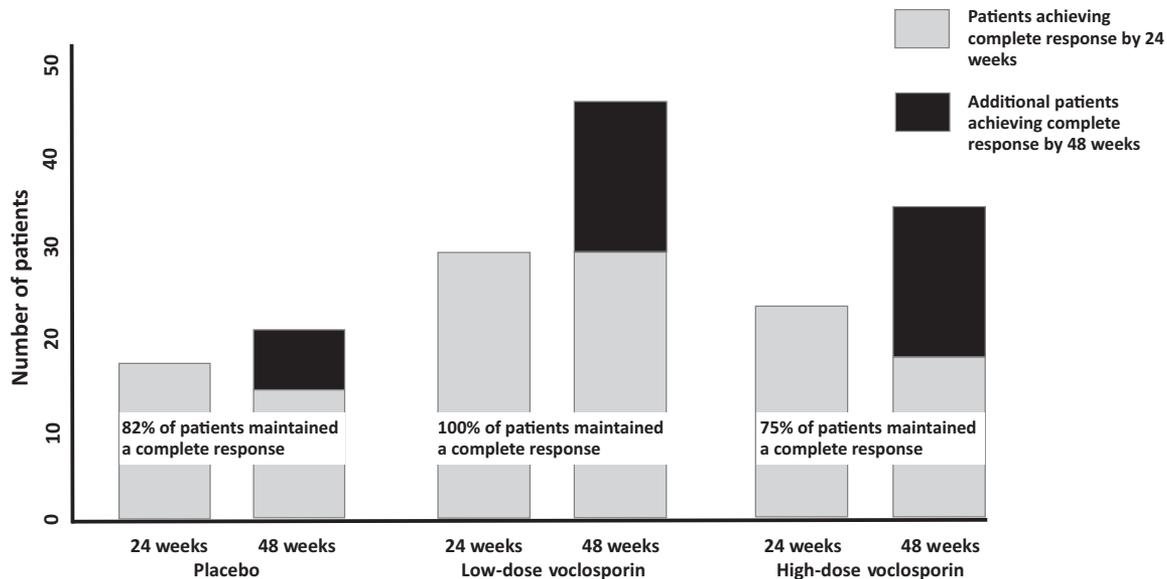
Low-Dose Voclosporin Week 48



High-Dose Voclosporin Week 48



**Figure 3 |** (continued) (CIs) were generated from a logistic regression model. The overall model was adjusted for biopsy class and mycophenolate mofetil (MMF) use at screening. Models for covariates also included terms for age, sex, race and region. *P* values test for the main effect of treatment within the given level of covariate. Subcont, subcontinent.



**Figure 4 | Durability of complete renal remission at 24 weeks.** The number of subjects who attained a complete renal remission at 24 weeks and maintained complete renal remission for an additional 24 weeks are shown (gray bars). Patients who did not achieve complete renal remission by 24 weeks but who did by 48 weeks are also shown (black bars).

stranded (ds) DNA antibody at weeks 24 and 48 in the low-dose VCS group and at weeks 12, 24, and 48 in the high-dose VCS group ( $P < 0.01$ ). At 48 weeks, anti-dsDNA antibody levels fell 7% in the placebo group, 51% in the low-dose VCS group, and 38% in the high-dose VCS group. A greater overall improvement in SLE activity in the VCS groups was also demonstrated by changes in Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) scores. At week 48, more than one-half of the subjects in the placebo group (53.4%) still had SELENA-SLEDAI scores  $>6$  compared with 29.2% and 40.9% in the low- and high-dose VCS groups, respectively. Although the improvements in the SELENA-SLEDAI scores were primarily due to improvements in the renal components, when extrarenal elements were assessed alone, the VCS groups tended to have a similar or greater reduction in activity than did the control group (Supplementary Figure S4). For example, the extrarenal

SELENA-SLEDAI scores fell 53%, 51%, and 67% in placebo, low-dose VCS, and high-dose VCS patients at week 48, respectively.

**Safety/adverse events**

Adverse events (AEs) are summarized in Tables 2 and 3. The majority of AEs and serious AEs occurred within the first 24 weeks of the study. The incidence of AEs and treatment-related AEs increased with high-dose VCS subjects, but serious AEs were observed in more low-dose VCS subjects (28.1%) compared with the high-dose VCS (25.0%) and placebo (15.9%) groups. The most frequent AEs in all groups were infections, followed by gastrointestinal disorders. Regarding treatment-related AEs, a higher incidence of *Investigations* was found, which is a code reflecting the need to assess estimated glomerular filtration rate (eGFR). The protocol mandated assessment of eGFR for any change in eGFR  $>10\%$ . This algorithm drove the increase in absolute treatment-related AEs. The actual impact on renal function is discussed later in this article. As specified in the protocol, patients experiencing a change in eGFR were closely monitored to ensure that the dose of VCS was decreased or that VCS was temporarily held. All patients were then monitored according to the protocol-defined schedule even if the study drug was permanently discontinued. This practice ensured completeness of not only efficacy but safety data. The next most common related AE was infection, without a substantial increase in serious infections across arms or a preponderance of any single infection leading to a safety concern.

Thirteen subjects died during the study, and unexpectedly, an imbalance of deaths was found between the treatment groups. More deaths occurred in the low-dose VCS group ( $n = 10$ , 11.2%) than in the high-dose VCS ( $n = 2$ , 2.3%) or placebo

**Table 2 | Overall summary of adverse events (safety set, N = 265)**

Distribution across categories of AE	Placebo (N = 88) n (%)	Voclosporin 23.7 mg BID (N = 89) n (%)	Voclosporin 39.5 mg BID (N = 88) n (%)
Any AE	75 (85.2)	82 (92.1)	85 (96.6)
Any serious AE	14 (15.9)	25 (28.1)	22 (25.0)
Any treatment-related AE	15 (17.0)	45 (50.6)	55 (62.5)
Any serious treatment-related AE	1 (1.1)	4 (4.5)	7 (8.0)
Any AE leading to study drug discontinuation	9 (10.2)	16 (18.0)	14 (15.9)
Any AE with outcome of death	1 (1.1)	10 (11.2)	2 (2.3)

AE, adverse event; BID, twice daily.

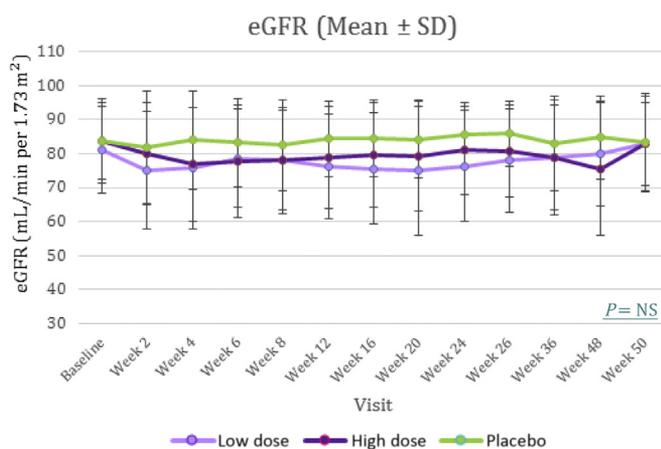
**Table 3 | Serious adverse events reported by >2% of subjects in any treatment group (safety set, N = 265)<sup>a</sup>**

Serious AEs reported by >2% of subjects in any treatment group	Placebo	Voclosporin	Voclosporin
	(N = 88)	23.7 mg BID	39.5 mg BID
	n (%)	(N = 89)	(N = 88)
	n (%)	n (%)	n (%)
Infections and infestations	7 (8.0)	11 (12.4)	12 (13.6)
Pneumonia	2 (2.3)	5 (5.6)	3 (3.4)
Urinary tract infection	0 (0.0)	2 (2.2)	1 (1.1)
Gastroenteritis	1 (1.1)	1 (1.1)	2 (2.3)
Sepsis	0 (0.0)	1 (1.1)	2 (2.3)
Renal and urinary disorders	1 (1.1)	5 (5.6)	1 (1.1)
Renal failure acute	0 (0.0)	4 (4.5)	1 (1.1)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	5 (5.6)	1 (1.1)
Pulmonary embolism	0 (0.0)	2 (2.2)	1 (1.1)
Acute respiratory distress syndrome	0 (0.0)	2 (2.2)	0 (0.0)
Nervous system disorders	1 (1.1)	4 (4.5)	3 (3.4)
Posterior reversible encephalopathy syndrome	0 (0.0)	2 (2.2)	2 (2.3)
Gastrointestinal disorders	1 (1.1)	2 (2.2)	2 (2.3)
Vascular disorders	0 (0.0)	2 (2.2)	2 (2.3)
Hypertension	0 (0.0)	2 (2.2)	2 (2.3)
Cardiac disorders	2 (2.3)	2 (2.2)	1 (1.1)
Musculoskeletal and connective tissue disorders	2 (2.3)	1 (1.1)	2 (2.3)
Systemic lupus erythematosus	2 (2.3)	1 (1.1)	2 (2.3)
Blood and lymphatic system disorders	2 (2.3)	1 (1.1)	0 (0.0)

AE, adverse event; BID, twice daily.

<sup>a</sup>Results presented here do not include additional serious adverse events that occurred after completion of the study: 3 deaths and 1 malignancy.

(n = 1, 1.1%) groups. The details and causes of each death are shown in [Supplementary Table S3](#). Most deaths (9/13) occurred within the first 2 months of entering the study. Between 6 and 12 months, only one death occurred in a patient treated with



**Figure 5 | Kidney function over time.** For each group, kidney function was measured via an estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. All raw eGFR values >90 ml/min per 1.73 m<sup>2</sup> were considered equal to 90 ml/min per 1.73 m<sup>2</sup>. Voclosporin was discontinued at week 48. NS, Not significant.

VCS. More than one-half of the deaths (7/13) occurred at 2 sites in Bangladesh. Possibly relevant to the imbalance in deaths, 2-fold more patients were randomized to low-dose VCS than placebo at these 2 sites. Similarly, in Sri Lanka, where 2 deaths occurred in patients treated with low-dose VCS, 4-fold more patients had been randomized to low-dose VCS than placebo.

Kidney dysfunction, hyperkalemia, diabetes, and an increase in blood pressure are well-known adverse effects of CNIs. A small decrease in mean eGFR was observed in the 2 VCS groups during the treatment period; however, within 2 weeks of the study conclusion, mean eGFR levels returned to baseline ([Figure 5](#)). Two patients who received placebo, 3 patients treated with low-dose VCS, and 3 patients treated with high-dose VCS withdrew from the AURA-LV study because of a >30% decrease in eGFR. Mean blood pressure decreased from baseline in all 3 treatment groups and remained lower than baseline for the duration of the study ([Supplementary Figure S5](#)). VCS had little impact on serum potassium levels ([Supplementary Figure S6](#)), and no one withdrew from the study because of hyperkalemia, with similar results for hypomagnesemia. Diabetes was reported in one patient who received placebo and in one patient who received low-dose VCS.

After study completion, a safety follow-up was conducted with subjects from the AURA-LV study to determine their status 3 to 6 months after the last subject completed the study. Three deaths were reported in the placebo group, and no further deaths were seen in the VCS groups ([Supplementary Table S4](#)).

## DISCUSSION

The initial treatment used for patients with active LN is high-dose corticosteroids plus MMF or cyclophosphamide. The 6- and 12-month CRR of these therapies are modest at best.<sup>11</sup> For example, the 6-month CRR in the Aspreva Lupus Management Study trial was 8.6%, and in the Lupus Nephritis Assessment with Rituximab trial it was approximately 22%; in both of these trials the target MMF dose was 3 g/d.<sup>12,13</sup> Borrowing from extensive experience in solid organ transplantation, where CNIs are successfully added to other immunosuppressive agents to prevent organ rejection, we combined VCS, a novel CNI, with a modest dose of MMF (2 g/d) and a low dose of corticosteroids and have shown that this approach is superior to MMF plus corticosteroids alone in inducing CRR at 24 weeks (low-dose VCS) and 48 weeks (low- and high-dose VCS). These data are consistent with a large trial from China that also showed a significantly higher 24-week CRR after induction with tacrolimus plus MMF and corticosteroids compared with cyclophosphamide plus corticosteroids.<sup>8</sup> However, our trial is the first to demonstrate efficacy in a multi-ethnic global cohort, suggesting that CNI-based treatment may be applicable to all patients with LN. This finding will need to be confirmed in another study because the percentage of black and Hispanic patients, who historically are less responsive to treatment, was low in the Aura-LV study. Furthermore, the VCS-treated subjects maintained a significantly

greater proportion of CRR after 48 weeks of treatment compared with the placebo group. In contrast, after 1 year of follow-up, the proportion of CRR was similar in the control group and the tacrolimus group in the Chinese LN cohort.<sup>14</sup> Although more data are needed, this finding may suggest that compared with conventional CNIs, VCS may have an additional therapeutic advantage in persons with LN.

Our CRR data at weeks 24 and 48 suggest that 7.5 and 3.9 patients with LN, respectively, would need to be treated with VCS to achieve one additional CRR. That is, if 3.9 patients are treated until week 48, one additional CRR would be achieved compared with administration of standard of care for those 3.9 patients.

Patients with a Class V component (pure Class V or Class III/IV+V) did not show an improvement in CRR upon treatment with VCS. This finding was unexpected and different from the finding observed in Chinese LN cohorts treated with CNI-based regimens. Because this trial included so few pure Class V patients (15%), all Class V patients were analyzed together. One possible explanation for the lack of benefit may be that Class III/IV+V patients take longer to achieve CRR.

Despite using 2 different doses of VCS, no apparent dose-response effect on therapeutic efficacy was observed. The reason for this finding is unclear, but the finding may indicate that the attained 6-month response rates are as high as can be expected in a multi-ethnic LN population. This argument is indirectly supported by other trials such as the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study and the Lupus Nephritis Assessment with Rituximab trial, in which only 20% to 30% of subjects achieved a CRR at 24 weeks.<sup>13,15</sup> In contrast, 6-month CRR rates reported in Chinese cohorts are much higher, suggesting that the magnitude of an early response may depend on race and ethnicity.<sup>8</sup> Because renal response in LN is defined mainly by the resolution of proteinuria, the rate of response likely depends on the severity of damage to the glomerular basement membrane and podocytes. It is conceivable that rapid responders have less structural damage and quickly repair the basement membrane to attenuate protein loss. Alternatively, adherence to high-dose VCS could have been lower if adverse effects were more severe, although this possibility is not borne out by the number of patients who withdrew from the trial as a result of adverse events.

Most categories of adverse events were more common in the patients treated with VCS compared with the placebo group. Although far more treatment-related adverse events occurred in the VCS groups, only 4 and 7 serious treatment-related events occurred in the low- and high-dose groups, respectively, compared with 1 in the patients who received placebo. Although overall mortality (4.9%) was similar to that of other recent LN trials<sup>12,16</sup> and consistent with disease severity and use of immunosuppression, the number of deaths was higher with low-dose VCS. It is difficult to account for this imbalance in mortality. The observation that mortality was higher in the low-dose than in the high-dose VCS group suggests reasons beyond simply the addition of VCS. Most of the deaths occurred at a few sites, and despite

effective randomization globally, more patients in these sites were treated with low-dose VCS than with placebo, which may account for why deaths were not more evenly distributed between patients treated with VCS and patients who received placebo at these sites. An important observation from the mortality data was that most deaths occurred very early in the trial. This information suggests that patients treated with VCS, MMF, and corticosteroids need careful follow-up for adverse events early in the course of treatment when severe events appear to be more frequent.

The number of serious AEs, including 5 episodes of acute kidney injury, was also higher in both groups of patients treated with low- and high-dose VCS. The excess of serious AEs in the low-dose VCS group may be accounted for by multiple events that occurred in subjects almost exclusively from the Indian subcontinent who ultimately died. Analysis of survivors revealed similar event rates between study arms. Nonetheless, this multiple-drug regimen for LN does require very close monitoring for AEs.

The design of the AURA-LV study included corticosteroids that were administered in a lower dose and were more rapidly tapered than in most LN trials. Initial dosing was equivalent to prednisone, 0.4 mg/kg/d, with a 12-week taper to 2.5 mg/d. Despite this abbreviated steroid course, the CRR of the AURA-LV placebo group at 24 and 48 weeks compared favorably with the CRR rates reported for other recent multi-ethnic LN trials,<sup>12,13,15–17</sup> suggesting that the low steroid background did not compromise efficacy. Concern that higher corticosteroid dosing in persons with SLE and LN is detrimental has been advanced by several investigators, and a handful of trials have shown that corticosteroids could be reduced or avoided in persons with LN.<sup>18,19</sup>

Although the results of the AURA-LV trial are encouraging, questions regarding CNI use remain. The optimal duration of therapy needs to be determined. In LN and other glomerular diseases, relapse rates are high after CNI discontinuation. This outcome was observed in the Chinese CNI maintenance trial, with LN flares beginning after the dose of tacrolimus was reduced.<sup>14</sup> In contrast, in the AURA-LV trial, assessment of proteinuria 2 weeks after stopping VCS showed no rebound effect.

Reduction of proteinuria is a major component of all currently accepted remission criteria for LN. In several studies, reduction of proteinuria during the first year of LN therapy has been associated with good long-term renal function and survival.<sup>20,21</sup> Underlying the relationship between proteinuria and renal remission is the assumption that resolution of proteinuria reflects resolution of inflammatory kidney injury—that is, histologic remission. However, serial kidney biopsy studies of patients with LN show that histologic and clinical remissions are discordant.<sup>22,23</sup> Furthermore, the therapeutic effects of CNIs are unique. Although these agents are immunomodulatory, they also can decrease proteinuria directly by altering renal hemodynamics and by facilitating the repair of podocyte foot processes,<sup>24–27</sup> which raises the question of what a reduction in proteinuria means for

patients with LN who are treated with CNIs. In the Chinese trial of tacrolimus plus MMF, a handful of repeat kidney biopsies performed after 6 months of treatment showed a good histologic response in the patients treated with CNI.<sup>8</sup> Furthermore, in the Chinese trial and the AURA-LV trial, other indicators of SLE activity, such as complement levels, autoantibody levels, and SLEDAI extrarenal activity indices also improved in the CNI groups to the same or greater extent than in the control groups. Taken together, these findings suggest that the CNIs attenuate immune-mediated renal injury in persons with LN.

Because of the encouraging data of the AURA-LN trial, the VCS regimen has now moved to a phase 3 randomized, placebo-controlled trial (Aurinia Renal Response in Active Lupus With Voclosporin [AURORA], NCT03021499) that will be up to 3 years in duration and will include a voluntary repeat biopsy option with central nephropathology assessment and molecular analyses. This trial will allow us to address the important issues of how CNIs improve treatment efficacy in persons with LN.

In summary, in this phase 2 multicenter placebo-controlled trial of VCS for the treatment of active LN, low-dose VCS was superior to placebo when combined with MMF and corticosteroids for induction of CRR. No improvement in efficacy occurred with high-dose VCS. VCS was generally well tolerated, but additional AEs often associated with CNIs occurred in the VCS groups. More deaths were observed in the low-dose VCS group, and although this outcome is difficult to explain, it mandates careful surveillance when this regimen is first initiated, because most deaths occurred very early. Further clinical assessment will be needed to determine whether VCS is superior in safety, efficacy, and pharmacokinetic and pharmacodynamic profiles compared with other CNIs and whether VCS should be used as a treatment for active LN.

## METHODS

### Study design and oversight

AURA-LV (NCT02141672) was a phase 2, multicenter, randomized, prospective, double-blind, placebo-controlled study of VCS versus matching placebo on a background of MMF and corticosteroids in patients with active LN. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. Institutional review boards at the participating centers approved the protocol, and all patients or their representatives provided written informed consent. The study was conducted in accordance with the protocol and amendments and was funded by Aurinia Pharmaceuticals Inc, Victoria, Canada.

### Study participants

Subjects aged 18 to 75 years who fulfilled at least 4 American College of Rheumatology criteria for SLE and had a kidney biopsy showing active Class III, IV or V LN within 6 months of screening were eligible for the AURA-LV trial. A potential limitation of the study was that kidney biopsies were read locally and not by a central nephropathologist. Subjects with Classes III and IV LN were required to have a UPCr  $\geq 1.5$  mg/mg in 2 consecutive, first morning void urine

specimens, whereas subjects with pure Class V LN were required to have a UPCr  $\geq 2$  mg/mg (Table 1). Patients with an eGFR based on the Chronic Kidney Disease Epidemiology Collaboration equation<sup>28</sup>  $\leq 45$  ml/min per 1.73 m<sup>2</sup> or serum potassium  $>5.5$  mmol/L at screening were excluded.

Prior treatment for LN is outlined in Supplementary Table S1. Patients could not have received biologic drugs within 3 months or cyclophosphamide within 1 month of screening.

### Treatment protocol

Eligible subjects were randomized at baseline to receive low-dose VCS (23.7 mg twice daily), high-dose VCS (39.5 mg twice daily) or low- or high-dose matched placebo in a ratio of 2:2:1:1, stratified by biopsy class (Class V vs. others) and by MMF use at screening. There was a randomization block size of 6, and kit numbers were a 5-digit number. Randomized patients were assigned the next available sequential kit number globally via a centralized Interactive Web Response System. VCS and placebo capsules were identical in taste, smell, and appearance. All study personnel and subjects were blind to the study drug administered using a double-blind method. To preserve the double-blind design, subjects randomized to the placebo group were matched to the active dosage groups. One-half of the subjects in the placebo group ( $n = 43$ ) were randomized to receive a total of 6 capsules per day, and one-half were randomized to receive a total of 10 capsules per day. The dosing schedule in the placebo group was the same as that of the active treatment groups. To this end, the double-blind nature of this trial preserves the blind with respect to active treatment and placebo.

Study treatment was continued for 48 weeks in all patients who completed the study, even if a CRR was achieved. Adherence was evaluated by pill counts at each visit and was estimated at 96.6%. All subjects received initial treatment with i.v. methylprednisolone, 0.5 g/d on days 0 and 1, before beginning a forced oral prednisone taper on day 2. Prednisone was started at 20 mg/d for subjects weighing  $<45$  kg and 25 mg/d for subjects weighing  $\geq 45$  kg, and it was reduced according to the protocol schedule (Figure 1). The novel aspect of the tapering schedule was the requirement that prednisone be decreased to 2.5 mg/d at week 16, which was achieved in 75% of patients in each study arm. Failure was declared if patients needed  $>10$  mg/d prednisone for 3 consecutive days or more than 7 total days between weeks 16 and 26. Patients who were taking MMF upon entering the study continued to take the preexisting dose. All other subjects began taking MMF at a dose of 1g/d, which was increased to 2 g/d after 1 week.

At every scheduled visit, eGFR (Chronic Kidney Disease Epidemiology Collaboration) was measured. The study drug was withheld if the eGFR fell by more than 30% relative to baseline. If the decrease in eGFR could not be explained by factors other than treatment, subjects stopped taking the drug but continued follow-up visits.

An automated blood pressure monitoring device was used for all blood pressure measurements when possible. After week 4, the target systolic pressure was  $\leq 130$  mm Hg, and the target diastolic pressure was  $\leq 80$  mm Hg. Investigators were required to use all means possible as permitted in the protocol to maintain the blood pressure below these limits, without changing angiotensin converting enzyme inhibitor/angiotensin-receptor blocker doses.

To determine sample size, a 20% CRR for control subjects was assumed. At a 2-sided  $\alpha$  level of 0.05, 86 subjects per arm were needed for 81% power to detect a doubling (to  $>40\%$ ) in CRR for either VCS arm (OR = 2.78). The proportion of subjects achieving CRR at week 24 was determined for each treatment group and the

relative remission rates for each active treatment group were compared with placebo (low and high dose combined). Proc power in SAS (Cary, NC) was used to generate the sample size. The test is a likelihood ratio  $\chi^2$  test for 2 proportions. The calculated sample size was adjusted using a continuity correction.

### Outcomes

The primary endpoint for the AURA-LV trial was the proportion of CRR at 24 weeks. CRR was defined as a decrease in UPCR to  $\leq 0.5$  mg/mg in 2 consecutive, first morning void urine specimens, plus an eGFR  $>60$  ml/min per  $1.73$  m<sup>2</sup> or no decrease of  $\geq 20\%$  of baseline eGFR on 2 consecutive occasions. Subjects who either died, received a rescue medication for SLE during the study, or were given  $>10$  mg prednisone for more than 3 consecutive days or for more than 7 total days from weeks 16 to 26 were declared treatment failures. Prednisone was increased in only 2 study patients, one in each of the VCS arms. A key secondary endpoint was the CRR rate at 48 weeks. Extrarenal lupus activity was assessed by the SELENA-SLEDAI score at baseline and at weeks 24 and 48.

AEs were aggregated by system, organ class, and preferred term and are presented as summary tables. Laboratory values (based on results from the central laboratory), vital signs, and other safety parameters were summarized by visit as absolute values and change from baseline.

An independent Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (hereafter referred to as the DSMB) was involved in study conduct and oversight and operated according to a written charter detailing well-defined operating procedures in accordance with the US Food and Drug Administration document *Guidance on the Establishment and Operation of Clinical Trial Data Monitoring Committees* (<https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm127073.pdf>). The DSMB was composed of a rheumatologist, a nephrologist, and a pharmaceutical physician with DSMB expertise. The DSMB's responsibilities included, but were not limited to, the following activities: reviewing collected data for indications of benefit or harm, reviewing sample size assumptions, and suggesting data analyses. The DSMB evaluated the progress of the study and assessed data quality and timeliness, participant recruitment, accrual and retention, and participant benefit versus risk. All safety data, including deaths that occurred during the study, were reviewed by the DSMB. The DSMB met 7 times and conducted 6 independent unblinded reviews of the data.

### Post-trial follow-up

Subjects were asked to remain in the study even after study drug was discontinued, and they adhered to this request very well, with the exception of those who withdrew consent ( $<10$  subjects in total). Long-term telephone follow-up is being performed on a 6- to 12-month basis (see [Supplementary Table S4](#)) to assess vital status. Response thus far has been excellent.

### Statistical analyses

The statistical analysis plan was prespecified and signed in advance of analyses. The primary endpoint (CRR) and other endpoints measured as rates were analyzed using logistic regression adjusting for the stratification factors of biopsy class and MMF use at screening. Results have been expressed as ORs and are presented with 95% CIs and *P* values. Covariate categories for complete remission were prespecified in the analysis plan, and odds of complete remission by covariate can be considered as a sensitivity analysis.

Time to endpoints were analyzed using Kaplan-Meier methodology and are presented in graphic format as a plot of survival probability against time. A Cox proportional hazards model adjusted for stratification variables was used to calculate hazard ratios. Deaths were handled as treatment failure.

Change from baseline variables (SELENA-SLEDAI, UPCR, serum albumin, anti-dsDNA, and complement levels) were analyzed using analysis of covariance, adjusting for baseline levels of the variable of interest.

## APPENDIX

### AURA-LV Site List

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**DISCLOSURE**

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**AUTHOR CONTRIBUTIONS**

BHR, NS, MAD, JT, and RBH conceived and designed the experiments; BHR, NS, WFP, MAD, JT, and RBH analyzed the data; BHR wrote the first draft of the manuscript; BHR, NS, WFP, MAD, JT, JRD, LL, SVH, and RBH contributed to the writing of the manuscript; BHR, NS, WFP, MAD, JT, JRD, LL, SVH, and RBH agreed with manuscript results and conclusions; BHR, NS, MAD, JT, and RBH jointly developed the structure and arguments for the article; BHR, NS, WFP, MAD, JT, JRD, LL, SVH, and RBH made critical revisions and approved the final version; all authors reviewed and approved of the final manuscript.

**SUPPLEMENTARY MATERIAL**

**Figure S1.** Disposition of study subjects.

**Figure S2.** Change in proteinuria and serum albumin over time.

**Figure S3.** Anti-dsDNA (A), C3 (B), and C4 (C) over time.

**Figure S4.** Mean change from baseline in nonrenal SELENA-SLEDAI score.

**Figure S5.** Systolic and diastolic blood pressure measurements over time.

**Figure S6.** Serum potassium levels over time.

**Table S1.** Summary of prior lupus nephritis treatment.

**Table S2.** Summary of concomitant medications reported for >10% of subjects.

**Table S3.** Causes of mortality in subjects with lupus nephritis.

**Table S4.** Retrospective follow-up of 252 subjects: lupus nephritis disease status.

Supplementary material is linked to the online version of the paper at [www.kidney-international.org](http://www.kidney-international.org).

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