Follow-up Kidney Biopsies from the AURORA 2 Clinical Trial Evaluating Voclosporin for the Treatment of Lupus Nephritis

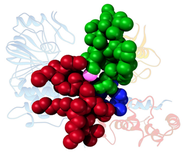
Samir V. Parikh[1], Clint Abner[2], Ernie Yap[2], Krista Piper[2], Rob Huizinga[3], Henry Leher[2]

[1]The Ohio State University Wexner Medical Center, Columbus, OH, United States, [2]Aurinia Pharmaceuticals Inc., Victoria, BC, Canada, [3]Reformation Consulting Services, North Saanich, BC, Canada

BACKGROUND

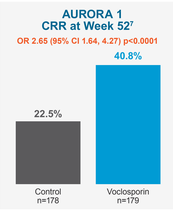
VOCLOSPORIN

- Voclosporin is a novel calcineurin inhibitor (CNI) approved in the United States, European Union, and Great Britain for the treatment of adults with lupus nephritis (LN)[1]
- Voclosporin has two complementary mechanisms of action relevant to the treatment of LN and the inhibition of calcineurin[1]:
  - Reduces activation of T-cells
  - Stabilizes podocytes, reducing proteinuria
- Voclosporin has a consistent dose-concentration relationship, eliminating the need for therapeutic drug monitoring[1,2]
- Unlike other CNIs, voclosporin has shown no increased safety signal for diabetes or dyslipidemia, and has no drug-drug interaction with mycophenolate mofetil (MMF)[3-8]



AURORA 1 AND AURORA 2

- The Phase 3 AURORA 1 study demonstrated that addition of voclosporin to MMF and glucocorticoids significantly increased complete renal response (CRR) rates at Week 52 in adult patients with active LN[7]
- The significant and meaningful reductions in proteinuria achieved in AURORA 1 were maintained for an additional two years in the Phase 3 AURORA 2 study[9]
- Mean estimated glomerular filtration rate (eGFR) remained stable over three years of treatment in AURORA 2
- Serious adverse event rates were similar between treatment arms with no unexpected safety events in AURORA 2

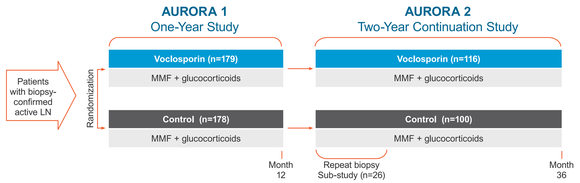


*CRR defined as urine protein creatinine ratio of ≤0.5 mg/mg, stable renal function (eGFR ≥60 mL/min/1.73 m^2 or no decrease >20% from baseline), presence of sustained, low-dose steroids (no more than 10 mg prednisone equivalent per day for ≥3 consecutive days or for ≥7 days in the eight weeks prior to the endpoint assessment), and no rescue medications. CI, confidence interval; CRR, complete renal response; eGFR, estimated glomerular filtration rate; OR, odds ratio.

METHODS

AURORA 1 AND 2 STUDY DESIGNS

- Patients that completed treatment in AURORA 1 were able to enroll in AURORA 2 and continue the same dose of blinded therapy (voclosporin or placebo) for an additional two years; all patients continued MMF and low-dose glucocorticoids at the same doses used at the end of AURORA 1
- Analysis of AURORA 2 patients provides efficacy and safety outcomes over three years of treatment with voclosporin compared to placebo



AURORA 1 enrolled patients with active LN, UPCR ≥1.5 mg/mg (≥2 mg/mg for Class V) and eGFR >45 mL/min/m^2. AURORA 1 patients were randomized to receive voclosporin (23.7 mg twice daily) or matching placebo, with MMF (target 2 g/day) and low-dose oral glucocorticoids. Protocol-defined glucocorticoid taper included intravenous methylprednisolone on Days 1 and 2. Oral glucocorticoid was initiated on Day 3 with 20-25 mg/day prednisone and tapered to a target dose of 2.5 mg/day at Week 16 and thereafter. Patients in AURORA 2 continued study drug (voclosporin or placebo), MMF, and glucocorticoids at the same doses used at the end of AURORA 1. eGFR, estimated glomerular filtration rate; LN, lupus nephritis; MMF, mycophenolate mofetil; UPCR, urine protein creatinine ratio.

HISTOLOGY SUB-STUDY

- The objective of the repeat biopsy sub-study was to further characterize the long-term impact of voclosporin on the kidney at the histologic level using repeat renal biopsies from a subset of patients participating in AURORA 1 and AURORA 2
- All patients in AURORA 1 had a baseline kidney biopsy prior to enrollment and repeat biopsies were performed in AURORA 2 after approximately 18 months of total treatment
- Blinded histopathologic grading was conducted by Arkana Laboratories and based on the National Institutes of Health (NIH) indices for LN activity and chronicity[10]
  - Activity scoring (scale 0-24) is based on the following variables: endocapillary hypercellularity, neutrophils/karyorrhexis, hyaline deposits, fibrinoid necrosis, cellular/fibrocellular crescents, interstitial inflammation
  - Chronicity scoring (scale 0-12) is based on the following variables: total glomerulosclerosis score, fibrous crescents, tubular atrophy, interstitial fibrosis

RESULTS

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

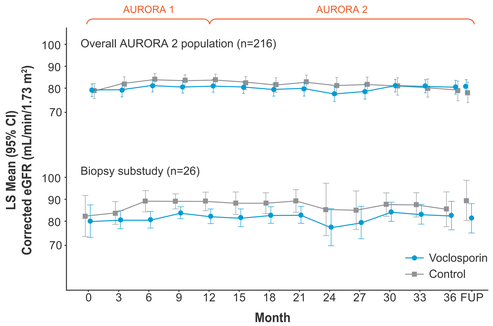
- Baseline and follow-up biopsy samples were collected from 16 patients in the voclosporin arm and 10 patients in the control arm
- Baseline demographics and clinical characteristics of patients in the biopsy sub-study were similar to those of the overall AURORA 1 population

	Biopsy Sub-study		AURORA 1
	Control n=10	Voclosporin n=16	Overall n=357
Age, years			
Mean (SD)	36.2 (12.1)	29.8 (8.6)	33.2 (10.96)
Sex, n (%)			
Female	9 (90)	15 (93.8)	313 (87.7)
Race, n (%)			
White	3 (30)	5 (31.3)	129 (36.1)
Asian	3 (30)	3 (18.8)	109 (30.5)
Black	0	0	34 (9.5)
Other*	4 (40)	9 (56.3)	85 (23.8)
Time since LN diagnosis, years			
Mean (SD)	6.0 (5.6)	3.3 (2.0)	4.6 (4.97)
Median	4.0	3.5	2.0
Biopsy Class, n (%)			
Class III/IV	6 (60)	13 (81.3)	215 (60.2)
Class V	1 (10)	1 (6.3)	50 (14.0)
Mixed Class III/V or IV/V	3 (30)	2 (12.6)	49 (24.9)
eGFR, mL/min/1.73 m^2			
Mean (SD)	95.7 (22.1)	100.8 (34.7)	91.2 (29.8)
UPCR, mg/mg			
Mean (SD)	4.7 (2.6)	4.6 (2.5)	4.0 (2.5)

eGFR, estimated glomerular filtration rate; LN, lupus nephritis; SD, standard deviation; UPCR, urine protein creatinine ratio. *Includes self-identified mixed race. Data from pretreatment baseline in AURORA 1 for n=10 patients in the control arm and n=16 patients in the voclosporin arm of the biopsy sub-study and the overall n=357 patients of AURORA 1.

eGFR OVER TIME

- Mean eGFR values over time in the biopsy sub-study were stable over three years and consistent with those observed in the larger AURORA 2 population



Renal function assessed with corrected eGFR (Chronic Kidney Disease Epidemiology Collaboration equation) using a prespecified ceiling of 90 mL/min/1.73 m^2. Data from n=10 patients in the control arm and n=16 patients in the voclosporin arm of the biopsy sub-study and the overall n=216 patients in AURORA 2. CI, confidence interval; eGFR, estimated glomerular filtration rate; FUP, follow-up; LS, least squares.

LABORATORY PARAMETERS, CLINICAL OUTCOMES, AND ACTIVITY AND CHRONICITY SCORES OVER TIME

- Baseline activity scores were similar between arms, with scores in both arms decreasing with treatment
- Chronicity scores were also similar between arms at baseline and remained stable over time
- Higher rates of both CRR and partial renal response (PRR) were observed in voclosporin-treated patients at Month 36
- There were no unexpected adverse events in patients treated with voclosporin, and the safety profile was consistent with the overall AURORA 2 population

	Control n=10		Voclosporin n=16	
	Baseline*	Follow-up	Baseline	Follow-up
Activity Index, mean (SD)	**2.8 (3.2)**	**0.4 (1.0)**	**1.8 (3.0)**	**0.4 (1.0)**
Chronicity Index, mean (SD)	**2.9 (2.3)**	**2.8 (2.7)**	**3.8 (3.5)**	**4.1 (3.3)**
	Baseline	Month 36	Baseline	Month 36
UPCR, mean (SD), mg/mg	4.71 (2.6)	2.1 (4.6)	4.59 (2.5)	0.99 (1.4)
eGFR, mean (SD), mL/min/1.73 m^2	82.6 (12.3)	85.8 (13.3)	80.3 (16.4)	82.7 (15.4)
CRR, % (n/n)	-	40.0 (4/10)	-	62.5 (10/16)
PRR, % (n/n)	-	70.0 (7/10)	-	81.3 (13/16)

CRR, complete renal response (defined as UPCR ≤0.5 mg/mg, stable eGFR, low-dose steroids, and no rescue medication); eGFR, estimated glomerular filtration rate; PRR, partial renal response (defined as reduction in UPCR of ≥50% from baseline); SD, standard deviation; UPCR, urine protein creatinine ratio. Histopathologic grading based on the National Institutes of Health indices for lupus nephritis activity (scale 0-24) and chronicity (0-12). Renal function assessed with corrected eGFR (Chronic Kidney Disease Epidemiology Collaboration equation) using a prespecified ceiling of 90 mL/min/1.73 m^2. *Data from pre-treatment baseline of AURORA 1.

MEAN SCORES FOR CHRONICITY INDEX VARIABLES

- All chronicity index variables remained stable from baseline to follow-up in both arms

	Control n=10		Voclosporin n=16	
	Baseline*	Follow-up	Baseline	Follow-up
Chronicity Index Variables, mean (SD)				
Global glomerulosclerosis	1.3 (1)	1.5 (1)	1.3 (1.4)	1.4 (1.2)
Fibrous crescents	0.2 (0.4)	0.1 (0.3)	0.4 (0.6)	0.2 (0.4)
Tubular atrophy	0.7 (0.7)	0.6 (1)	1.1 (1.1)	1.3 (1.2)
Interstitial fibrosis	0.7 (0.7)	0.6 (1)	1.1 (1.1)	1.2 (1.2)

SD, standard deviation. Histopathologic grading based on the National Institutes of Health index for lupus nephritis chronicity, with each variable scored on a scale from 0-3.

CONCLUSIONS

- This is the first study to assess histologic changes in the kidneys of patients with LN treated with voclosporin
- Exposure to voclosporin was not associated with chronic injury, with the average chronicity index remaining stable in both arms from baseline to follow-up
- Activity scores decreased in conjunction with improvements in urine protein creatinine ratio (UPCR) in both treatment arms
- Efficacy and safety results from this small subgroup were consistent with outcomes from the larger AURORA 2 study population

STUDY LIMITATIONS AND CONSIDERATIONS

- AURORA 2 was a continuation study of patients who elected to continue treatment following completion of AURORA 1, resulting in a selection bias of patients
- While patients in the biopsy sub-study were generally representative of the overall AURORA 1 cohort at baseline, the study included only a small number of patients with repeat biopsies in AURORA 2
- Interobserver variability occurs in the reading of biopsies, and histologic lesions associated with chronic disease are not specific to treatment with voclosporin

REFERENCES

1. LUPKYNIS® [package insert]. Rockville, MD: Aurinia Pharma U.S., Inc., 2021.
2. van Gelder T et al. J Am Soc Nephrol. 2020;31:594.
3. Busque S et al. Am J Transplant. 2011;11(12):2675-2684.
4. Kolic J et al. Endocrinology. 2020;(161)11.
5. van Gelder T et al. Nephrol Dial Transplant. 2021;gfab022.
6. Ardoin S et al. Kidney Int Rep. 2022;7:S99.
7. Rovin BH et al. Lancet. 2021;397(10289):2070-2080.
8. van Gelder T et al. Nephrol Dial Transplant. 2022;37(5):917-922.
9. Teng YKO et al. Nephrol Dial Transplant. 2022;37(3);gfac108.002.
10. Bajema IM et al. Kidney Int. 2018;93(4):789-796.

DISCLOSURES

SVP reports grant payments from EMD Serono and Aurinia Pharmaceuticals Inc, and consulting fees from Aurinia Pharmaceuticals Inc., GSK plc, Bristol-Myers Squibb, Kezar Life Sciences, and Alexion Pharmaceuticals.
RH reports consulting fees from Aurinia Pharmaceuticals Inc.
CA, EY, KP, and HL are employees and shareholders of Aurinia Pharmaceuticals Inc.
Editorial support provided by MediComm Partners Ltd.
Aurinia Pharmaceuticals Inc. provided funding for the study and presentation.

© 2023 Aurinia Pharmaceuticals Inc. All rights reserved.
Trademarks are the property of Aurinia Pharmaceuticals Inc.