Voclosporin Associated with a Statistically Significant 53% Reduction in Risk of Renal-Related Event or Death: A Post-Hoc Analysis of the AURORA 1 Phase 3 Study

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Background

- Voclosporin is a novel, structurally modified calcineurin inhibitor (CNI) immunosuppressant indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN).
- Voclosporin is the first US FDA-approved oral therapy for the treatment of LN.
- Voclosporin targets LN with a dual mechanism of action [1] (see Figure 1)
- Voclosporin has been studied in 3 clinical studies:
  - AURA-LV, a randomized Phase 2 Study in 265 patients (NCT02141672);
  - AURORA 1, a randomized Phase 3 study in 357 patients (NCT03021499) [2]; and
  - AURORA 2, a randomized Extension Study in 216 patients (NCT03597464).
- Voclosporin was granted full FDA approval based on a statistically significant and clinically meaningful improvement in Complete Renal Response (CRR) at Week 52 (40.8% for voclosporin vs. 22.5% for placebo; Odds Ratio=2.7 (95% CI: 1.6, 4.3); p<0.001) in AURORA 1 (See Figure 2)
- In AURORA 1, voclosporin also was associated with:
  - A statistically significant and meaningful improvement in CRR at Week 24 (32.4% for voclosporin vs. 19.7% for placebo; Odds Ratio=2.2 (95% CI:1.3, 3.7); p=0.002) (See Figure 2)
  - A rapid proteinuria reduction (See Figure 3)

Figure 1: Dual Mechanism of Action

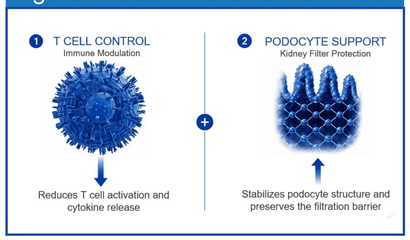
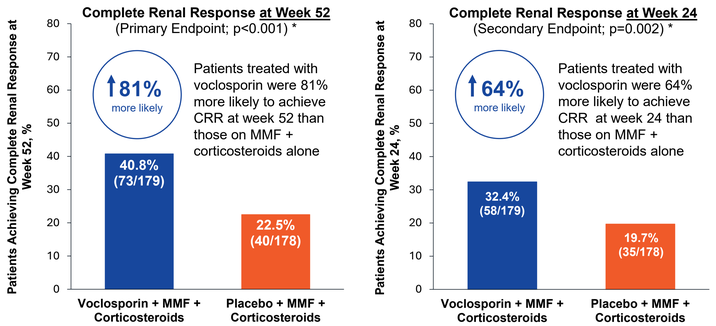
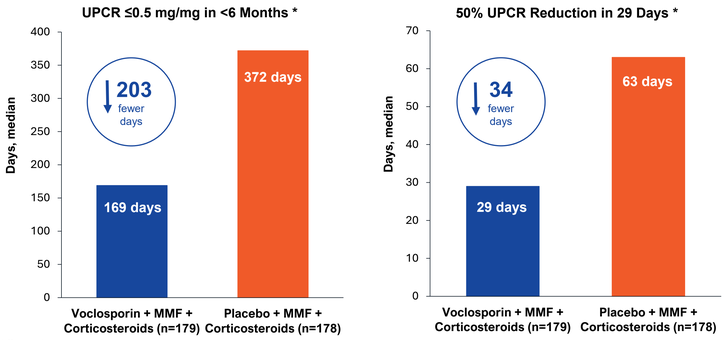


Figure 2: Improvement in CRR at Week 52 and Week 24



* CRR was defined as urine protein-to-creatine ratio (UPCR) of ≤0.5 mg/mg, stable renal function (defined as eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20%), no sustained corticosteroids and no administration of rescue medications

Figure 3: Rapid Proteinuria Reduction



* Secondary endpoint

Results

Objectives

- Time-to-event analyses in LN studies provide supplemental information beyond that provided by fixed time-point endpoints such as CRR.
- This post-hoc analysis of AURORA 1 investigated the composite endpoint of Time to Renal-Related Event or Death, a commonly measured key secondary endpoint in LN clinical studies, in patients treated with voclosporin compared to placebo.

Methods

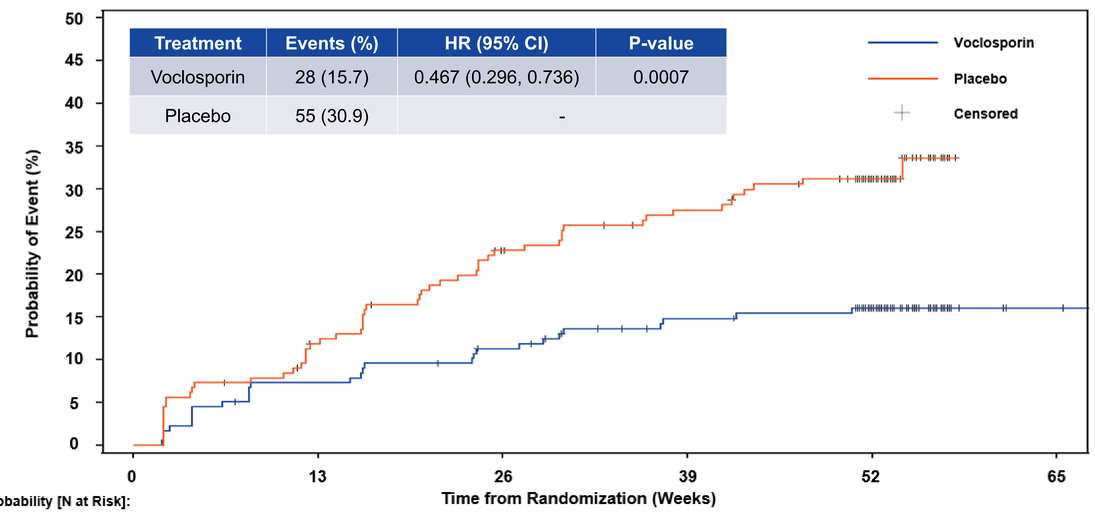
- In AURORA 1, patients were randomized to either voclosporin (23.7 mg) or placebo twice daily in combination with mycophenolate mofetil (target 2 g/day) and low-dose glucocorticoids (target ≤2.5 mg/day by Week 16) for 52 weeks.
- Time to Renal-Related Event or Death was analyzed by Kaplan-Meier method, and treatment arms were compared utilizing the log-rank test.

Risk of Renal-Related Event or Death

- A total of 356 patients (the safety population: voclosporin=178; placebo=178) were included in the analysis.
- Voclosporin was associated with a statistically significant 53% reduction in the risk of Renal Related Event or Death (Hazard Ratio=0.47; p=0.0007) (See Figure 4 and Table 1).
- Hazard Ratios also favored treatment with voclosporin (Hazard Ratios <0.5) for most of the individual components of the composite endpoint (death, treatment failure and worsening proteinuria) (See Table 1).
- The probability of worsening eGFR was similar in the two treatment arms (See Table 1).

Figure 4: Time to Renal-Related Event or Death *

Treatment	Events (%)	HR (95% CI)	P-value
Voclosporin	28 (15.7)	0.467 (0.296, 0.736)	0.0007
Placebo	55 (30.9)	-	



Probability [N at Risk]:						
Voclosporin	0.0 [178]	7.3 [164]	11.3 [154]	14.8 [142]	16.0 [117]	16.0 [2]
Placebo	0.0 [178]	11.8 [154]	22.8 [132]	27.5 [121]	31.1 [89]	

* Time to renal-related event or death is defined as the time to the first occurrence of death, treatment failure, worsening proteinuria or worsening eGFR

Table 1: Time to Renal-Related Event or Death

	Voclosporin 23.7 mg BID N=178 n (%)	Placebo N=178 n (%)	Hazard Ratio vs. Placebo HR (95% CI)
Time to Renal-Related Event or Death *			
Subjects with event	28 (15.7%)	55 (30.9%)	0.47 (0.30, 0.74)
Adverse Event			
Death	1 (0.6%)	5 (2.8%)	0.19 (0.02, 1.65)
Treatment failure **	17 (9.6%)	35 (19.7%)	0.45 (0.25, 0.81)
Worsening proteinuria ***	8 (4.5%)	33 (18.5%)	0.22 (0.10, 0.48)
Worsening eGFR ****	25 (14.0%)	23 (12.9%)	1.07 (0.61, 1.89)

* Time to Renal-Related Event or Death is defined as the time to the first occurrence of death, treatment failure, worsening proteinuria or worsening eGFR.
** Treatment failure is present if any of the following are met: 1) new End-Stage Renal Disease (ESRD) or need for chronic dialysis or renal transplantation, 2) clinically significant, sustained worsening in UPCR and/or eGFR from Week 24 onward that leads the investigator to conclude the subject has failed the randomized treatment period, or 3) receipt of rescue therapy, except corticosteroid-only rescue.
*** Worsening proteinuria is defined as a confirmed ≥ 50% increase in UPCR from baseline to a value ≥3 g/g.
**** Worsening eGFR is defined as a confirmed ≥30% decrease in eGFR from baseline to a value <60 mL/min/1.73 m^2.

Patient Baseline Characteristics

- A total of 356 patients were included in the safety analysis.
- Patient characteristics were well balanced at baseline (See Table 2).

Table 2: Patient Baseline Characteristics

	Voclosporin N=178	Placebo N=178
Age, mean (range) years	32.7 (18-62)	33.6 (18-72)
Gender, n (%)		
Female	160 (89.9)	152 (85.4)
Male	18 (10.1)	26 (14.6)
Biopsy class, n (%)		
Class III	20 (11.2)	29 (16.3)
Class IV	91 (51.1)	77 (43.3)
Class V	25 (14.0)	25 (14.0)
Mixed Class II and V	0 (0.0)	1 (0.6)
Mixed Class III and V	23 (12.9)	20 (11.2)
Mixed Class IV and V	19 (10.7)	26 (14.6)
UPCR (mg/mg), mean (SD)	4.1 (2.7)	3.9 (2.4)
eGFR (mL/min/1.73m^2), mean (SD)	92.1 (30.6)	90.4 (29.0)

Conclusions

- The AURORA 1 Phase 3 study demonstrates that, in addition to significant improvements in CRR:
  - Treatment with voclosporin is associated with a statistically significant 53% reduction in the risk of Renal-Related Event or Death (Hazard Ratio=0.47; p=0.0007), reinforcing voclosporin's favorable efficacy and safety profile; and
  - Hazard Ratios favored treatment with voclosporin (Hazard Ratios <0.5) for most of the individual components of the composite endpoint (death, treatment failure and worsening proteinuria).

References

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2. Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *The Lancet*. May 2021;doi:10.1016/S0140-6736(21)00578-X

Disclosures

Amit Saxena: AbbVie Inc., Amgen Inc., AstraZeneca PLC, Aurinia Pharmaceuticals Inc., Bristol Myers Squibb Company, Eli Lilly and Co., Genentech, Inc., GSK plc, Kezar Life Sciences, Inc., Synthekine, Inc., UCB S.A.; Ellen M Ginzler: None declared; Cristina Arriens: AstraZeneca PLC, Biogen Inc., Bristol Myers Squibb Company, Cabaletta Bio, Inc., Health & Wellness Partners, LLC, Synthekine, Inc.; Dawn Caster: Alexion Pharmaceuticals, Inc., Apellis Pharmaceuticals, Inc., AstraZeneca PLC, Aurinia Pharmaceuticals Inc., Cabaletta Bio, Inc., Calliditas Therapeutics AB, Dimerix Limited, GSK plc, Novartis AG, Roche Holding Ltd, Travere Therapeutics, Inc.; Juanita Romero-Diaz: GSK plc; Keisha Gibson: Travere Therapeutics, Inc.; Joshua Kaplan: Aurinia Pharmaceuticals Inc.; Sandra Navarra: AstraZeneca PLC, Biogen Inc., Otsuka Pharmaceutical Co., Ltd., Viatris Inc.; Samir Parikh: Alexion Pharmaceuticals, Inc., Aurinia Pharmaceuticals Inc., Autolus Therapeutics plc, Calliditas Therapeutics AB, GSK plc, Kezar Life Sciences, Inc., Otsuka Pharmaceutical Co., Ltd., Travere Therapeutics, Inc., Vera Therapeutics, Inc., Vertex Pharmaceuticals Inc.; Greg Keenan: Aurinia Pharmaceuticals Inc.; Stew Kroll: Aurinia Pharmaceuticals Inc.; Brad H. Rovin: Alexion Pharmaceuticals, Inc., AstraZeneca PLC, Aurinia Pharmaceuticals Inc., Biogen Inc., Bristol Myers Squibb Company, Genentech, Inc., GSK plc