Aurinia™

Renal Biopsy Sub-study

April 2023

Lupkynis® (voclosporin) capsules 7.9 mg

indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN)

Limitations of use: Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation

Renal Biopsy Sub-study

Background

- The clinical utility of LUPKYNIS, a novel, second generation CNI, in lupus nephritis has been established[1-3]
  - LUPKYNIS has shown higher rates of remission and response over 3 years in placebo-controlled clinical trials against a background of the then standard of care (SOC) while preserving renal function, without typical first-generation calcineurin inhibitor (CNI) clinical manifestations of toxicity
- First-generation CNIs, tacrolimus (TAC) and cyclosporine A (CsA), are known to cause irreversible, histopathologic kidney damage characterized by arteriolar hyalinosis, interstitial fibrosis, tubular atrophy or glomerular sclerosis[4]
  - The renal tissue-level impact of the LUPKYNIS has not been demonstrated to date

Biopsy Sub-study

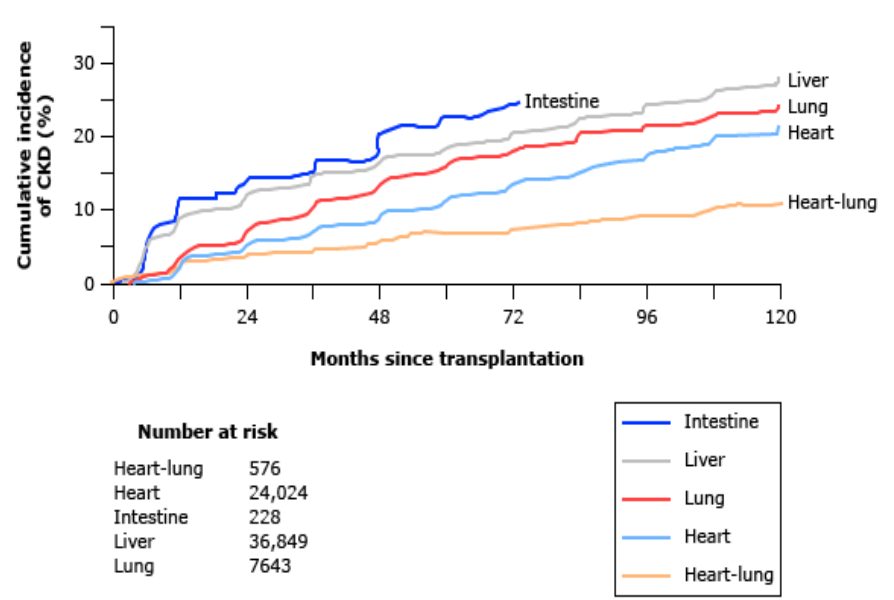
- Enrolled a representative cohort of the AURORA 1 study population
- Biopsy samples were scored using the validated National Institutes of Health (NIH) systematic approach to assessing disease activity (histologic measures of inflammation) and chronicity (irreversible kidney damage and scarring associated with end-stage kidney disease)[5,6]

1. Rovin BH et al. Lancet. 2021;397(10289):2070-2080. 2. Arriens C et al. Arthritis Rheumatol. 2022;74 (suppl 9). 3. Parikh S et al. Am Soc Nephrol. 2022;33: 184. 4. Naesens M et al. Clin J Am Soc Nephrol. 2009;4:481-508.
5. Bajema IM et al. Kidney Int. 2018;93(4):789-796. 6. Austin HA et al. Kidney Int. 1984; 25:689-695.

Nephrotoxicity Associated with First-Generation CNIs

- Patients treated with first generation CNIs are at higher risk of developing kidney injury. Most data on CNI nephrotoxicity pertains to CsA which has been available for a much longer time[1]
- CNI nephrotoxicity is manifested either as acute kidney injury, which is hemodynamic and largely reversible after reducing the dose, or as chronic progressive kidney disease, which is usually irreversible[1-4]
- Other kidney effects of the CNIs include tubular dysfunction and, rarely, a thrombotic microangiopathy that can lead to acute kidney allograft loss[1,4]
- However, a similar pattern of kidney injury from CsA is seen with the use of TAC, thereby suggesting a drug class effect[1-2]

Incidence of chronic kidney disease following nonrenal solid organ transplantation[3]

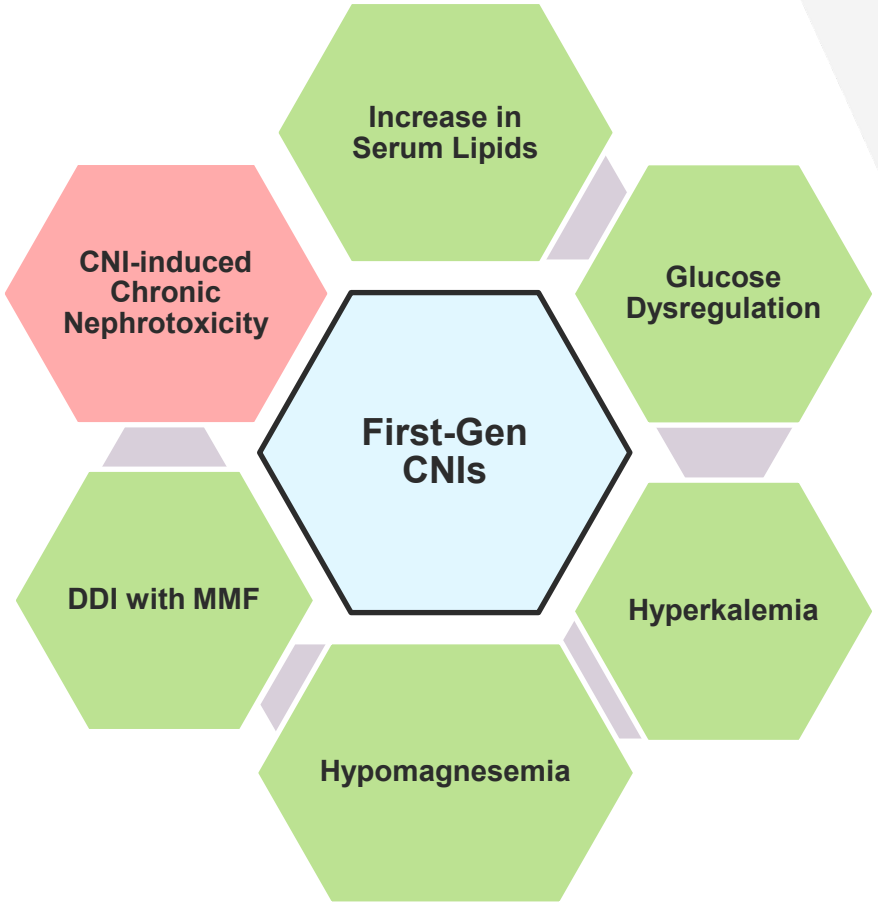


Cumulative incidence of CKD, defined as an estimated glomerular filtration rate <30 mL/min/1.73 m^2, among 69,321 people who received nonrenal solid organ transplants in the United States between 1990 and 2000.

1. Burdmann E et al. Seminar in Nephrology. 2003; 23(5):465-476. 2. Hardinger K et al. Kidney transplantation in adults: Maintenance immunosuppressive therapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 4, 2023). 3. Ojo AO et al. N Engl J Med. 2003;349(10):931-40. 4. Naesens M et al. Clin J Am Soc Nephrol. 2009;4:481-508.

Clinical Impact of First-Generation CNIs on Safety and Tolerability

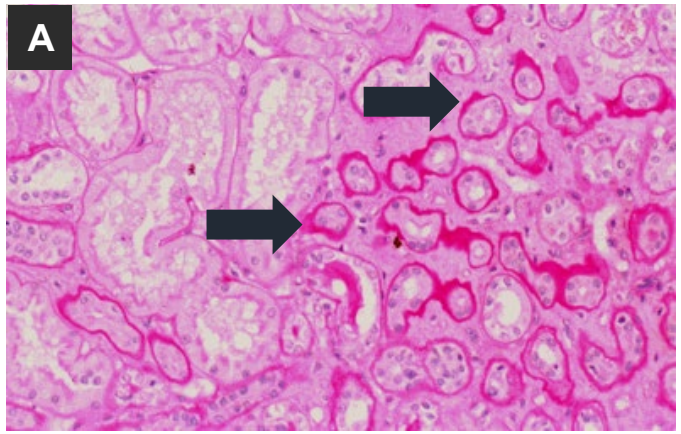
- Long-term safety data for first-generation CNIs in non-lupus nephritis conditions have created questions regarding safety associated with the long-term use of LUPKYNIS in patients with LN
- Several studies suggest LUPKYNIS does not possess many of the clinical safety considerations associated with first-generation CNIs
  - LUPKYNIS is a second-generation CNI without a therapeutic drug monitoring requirement[1]
  - **Lipid improvement:** CsA is associated with rapid and clinically important increases in serum lipid. LUPKYNIS has not and has been shown to reduce inflammatory lipids[2]
  - **No impact on mycophenolate:** CsA causes reduction in mycophenolate levels while LUPKYNIS has not caused such reductions[3]
  - **Electrolyte Impact:** First-generation CNIs may cause kidney tubular damage seen as hypomagnesemia and hyperkalemia. LUPKYNIS used in lupus nephritis has shown little to no impact[4]
  - **Diabetes Impact:** TAC has been associated with hyperglycemia, diabetes and islet cells death. In studies of lupus nephritis, LUPKYNIS has not had such associations[5]



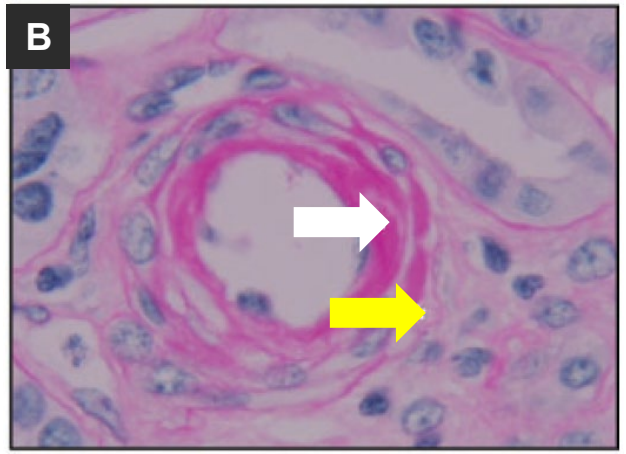
1. van Gelder T et al. Expert Rev Clin Pharmacol. 2022;15(5):515-529. 2. Afshinnia F et al. J Am Soc Nephrol. 2022;33: 792. 3. van Gelder T et al. Nephrol Dial Transplant. 2022;37:917-922. 4. Palmer B et al. Kidney International Reports. 2022;7(2):S175-6. 5. Kolic J et al. Endocrinology. 2020;161(11):bqaa162.

Characteristic Histopathology Associated with CNI-Nephrotoxicity

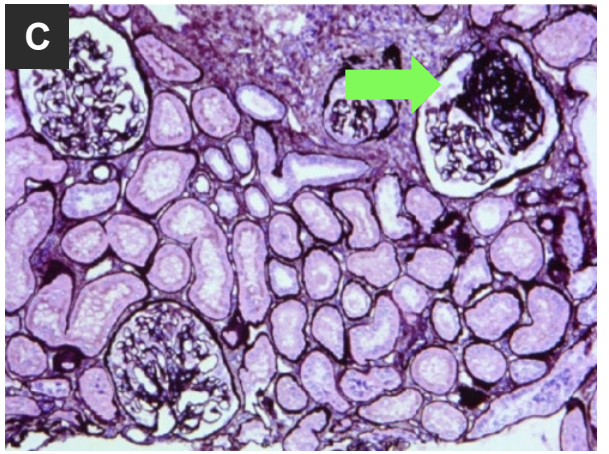
Light microscopy of CsA-induced fibrosis and atrophy[1]



Light microscopy of hyaline deposits of subendothelial and arteriolar media[2]



PAS staining of segmental glomerulosclerosis[3]

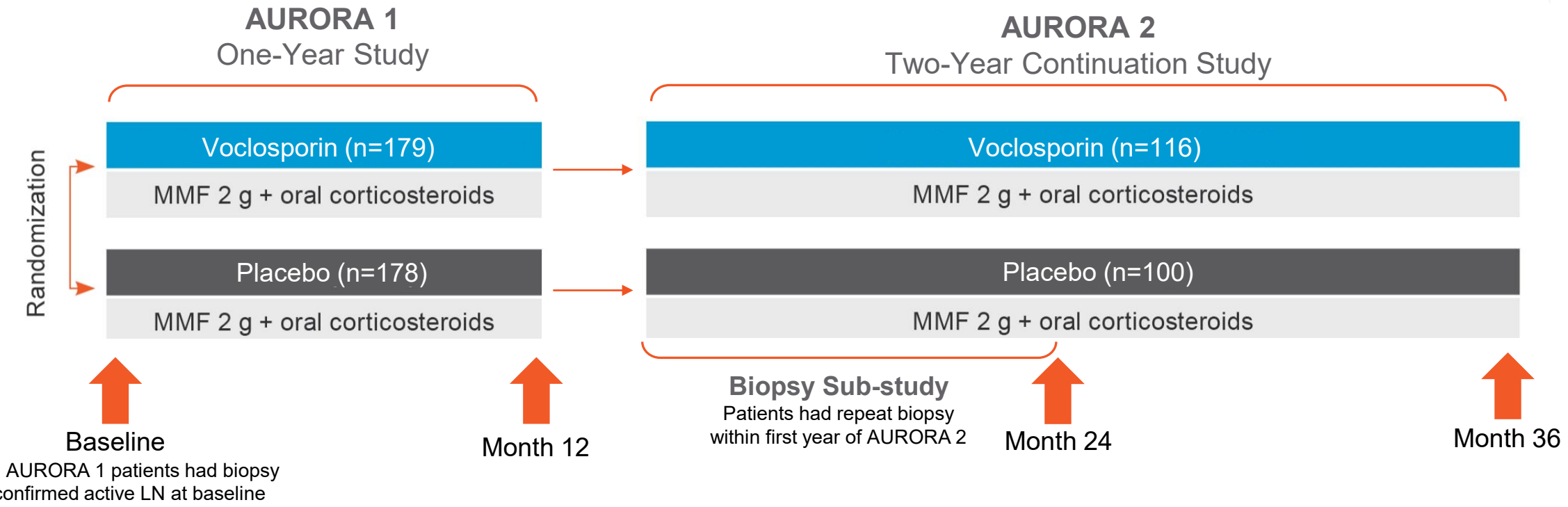


Histopathologic associations emerged from patients receiving solid-organ transplants with sequential biopsies. These were not controlled with patients who did not receive CNI therapy.

1. Hardinger K. Cyclosporine and tacrolimus nephrotoxicity. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 4, 2023). 2. Snanoudj R et al. Am J Transplant. 2011;11(12):2635-2646.
3. Han M-H, Kim Y-J. Biomed Res Int. 2016; 2016:9375753.

AURORA Biopsy Sub-Study

- AURORA 1 is the 357 patient, Phase 3, one-year, lupus nephritis study comparing LUPKYNIS to placebo, in combination with the then SOC
- AURORA 2 is the Phase 3, global, double-blind, two-year continuation study of AURORA 1; 216 patients enrolled into AURORA 2, providing LUPKYNIS exposure data of up to three years



LUPKYNIS Renal Biopsy Sub-Study Methods

- Twenty-six patients agreed to participate in the biopsy sub-study
  - 10 patients were in the standard of care treatment group
  - 16 patients were in the LUPKYNIS treatment group

- After approximately 18-months of treatment, participating patients underwent a follow-up kidney biopsy
  - Biopsies were processed utilizing standard processes and routine staining procedures
  - Biopsy slides were evaluated and scored by renal histopathologists at a specialized renal pathology laboratory according to the 2018 ISN/RPS guidelines[1]

1. Bajema IM et al. Kidney Int. 2018;93(4):789-796.

Biopsy Sub-study Patient Demographics Similar to the Main AURORA 1 Study

	Biopsy Sub-Study Patients		
	SOC n=10	LUPKYNIS n=16	AURORA 1 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)
Other*	4 (40)	9 (56.3)	119 (33.4)
Pretreatment eGFR, mL/min/1.73 m^2			
Mean (SD)	95.7 (22.1)	100.8 (34.7)	91.2 (29.8)
Pretreatment UPCR, mg/mg			
Mean (SD)	4.7 (2.6)	4.6 (2.5)	4.0 (2.5)

The sub-study population demonstrated clinical results consistent with that observed in the overall AURORA 1 and 2 populations

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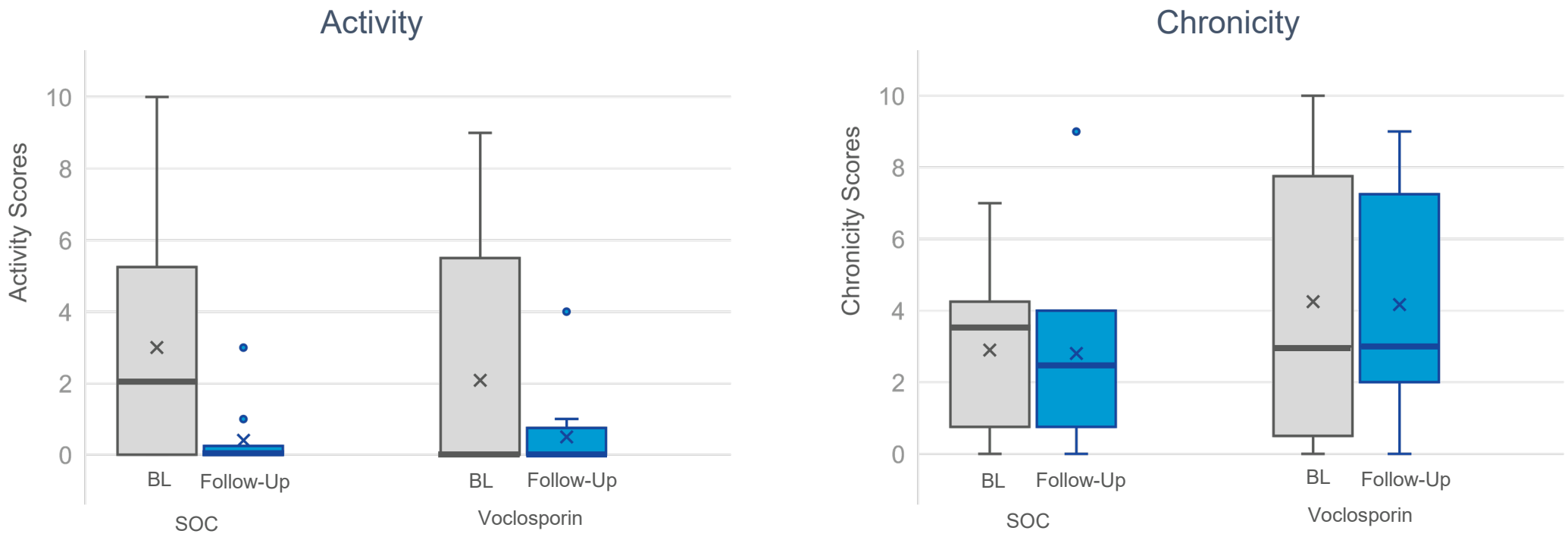
*Includes black and mixed race.
Data from pretreatment baseline in AURORA 1 for 16 patients in the voclosporin group and 10 patients in the standard of care (SOC) group of the biopsy sub-study and the overall 357 patients of AURORA 1.

LUPKYNIS Biopsy Study - NIH Scoring system

Activity Indices	Score
Endocapillary hypercellularity	0-3
Neutrophils / karyorrhexis	0-3
Hyaline deposits / wire loops	0-3
Fibrinoid necrosis	(0-3) x 2
Cellular or fibrocellular crescents	(0-3) x2
Interstitial inflammation	(0-3) x2
Total Score	0-24
Chronicity Indices	
Global glomerulosclerosis	0-3
Fibrous crescents	0-3
Tubular atrophy	0-3
Interstitial fibrosis	0-3
Total Score	0-12

1. Bajema IM et al. Kidney Int. 2018;93(4):789-796.

Biopsy Sub-study Histology Results



Overall, activity scores decreased, and chronicity scores were stable

Data from pretreatment baseline in AURORA 1 (i.e., BL) and after 15-18 months of study treatment (i.e., Follow-up) for 16 patients in the voclosporin group and 10 patients in the standard of care (SOC) group of the biopsy sub-study. Histopathologic grading based on the National Institutes of Health indices for lupus nephritis activity (scale 0-24) and chronicity (scale 0-12). Box plot of activity and chronicity scores are represented at BL and follow-up renal biopsies: x represents mean and horizontal bold line represents median. The top and bottom boxes represent the 75th and 25th percentiles. Outliers are represented as individual dots.

Conclusions

- Long-term use of first-generation CNIs such as cyclosporine and tacrolimus are associated with a variety of acute findings including renal dysfunction, glucose dysregulation, hyperkalemia, hypomagnesemia, drug-drug interactions with MMF, and serum lipid elevation
- Irreversible renal damage due to progressive tubulo-interstitial injury and glomerulosclerosis has been associated with exposure to chronic first-generation CNIs
- LUPKYNIS has shown higher rates of renal response over 3 years in placebo-controlled clinical trials against a background of the then SOC, while preserving renal function, without typical first-generation CNI clinical manifestations of toxicity

Conclusions Continued:

- The biopsy sub-study of a representative population demonstrated results consistent with the established clinical safety and efficacy of LUPKYNIS, a novel, second-generation CNI
- NIH disease activity scores, a histological measure of kidney inflammation, decreased substantially in both arms compared to baseline
- NIH chronicity scores, a histological measure of irreversible kidney damage and scarring, associated with end-stage kidney disease, were stable in both treatment groups
- The totality of the clinical and safety evidence in conjunction with these observations further differentiates LUPKYNIS
- Results to be presented at an upcoming scientific meeting
- We will submit these results to applicable regulatory authorities

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