Purpose To investigate changes in B cell subsets in relation to renal flares upon initiation of standard therapy (ST) plus belimumab or placebo in patients with systemic lupus erythematosus (SLE).

Methods We analysed data from the BLISS-76, BLISS-SC and BLISS Northeast Asia trials. Circulating CD19+ B cell subsets were characterised through flow-cytometry. We investigated the associations of relative to baseline rapid (through week 8) and early (through week 24) percentage changes in circulating B cell subsets, anti-dsDNA antibodies and complement levels with the occurrence of at least one renal flare during follow-up.

Results Patients who developed renal flares showed a more prominent rapid decrease in CD19+CD20+CD138+ short-lived plasma cells (-50.4% versus -16.7%; P=0.019) and CD19+CD20-CD27bright plasmablasts (-50.0% versus -29.9%; P=0.020) compared with patients who did not flare, followed by a subsequent return to near-baseline values, while patients who did not flare showed gradual yet non-significant decreases in these cell subsets. Remarkably, more prominent rapid reductions in CD19+CD20-CD138+ long-lived plasma cells were associated with a protection against renal flares in belimumab-treated patients (-11.3% versus -29.2%; OR: 1.16; 95% CI: 1.03–1.32; P=0.019), while changes in long-lived plasma cells did not differ between patients who developed renal flares and patients who did not in the subgroup treated with ST alone. Rapid and early changes in anti-dsDNA or complement levels showed no clear association with renal flares.

Conclusions An initial decrease followed by a subsequent return in circulating short-lived plasma cells and plasmablasts upon treatment for active SLE portended renal flares, indicating a need for therapeutic adjustments in selected patients. Rapid decreases in long-lived plasma cells upon belimumab therapy commencement may signify a greater protection against renal flares.

S06.2 LONG-TERM EFFICACY AND SAFETY OF VOCLOSPORIN WITH MMF AND LOW-DOSE STEROIDS: DATA FROM THE AURORA 2 CONTINUATION STUDY

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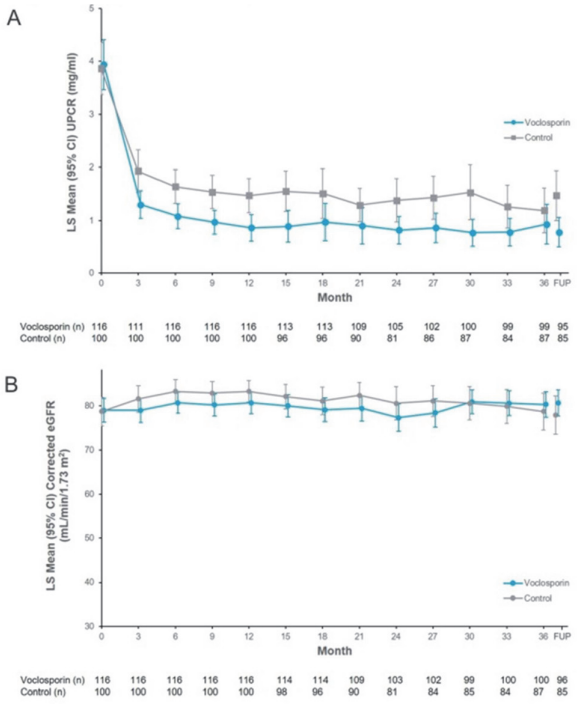
Purpose Voclosporin is a novel calcineurin inhibitor approved in the United States in January 2021 for the treatment of adult patients with active lupus nephritis in combination with background immunosuppressive therapy. The Phase 3 AURORA 1 study showed that adding voclosporin to mycophenolate mofetil (MMF) and low-dose steroids led to significantly greater reductions in proteinuria at 52 weeks. Given the potentially serious safety concerns associated with the long-term use of oral steroids, we evaluated the safety and efficacy of treatment with voclosporin in patients maintained on low-dose steroids for an additional 24 months in the AURORA 2 continuation study.

Methods Key inclusion criteria for the parent AURORA 1 study included biopsy-proven active lupus nephritis (Class III, IV, or V ± III/IV), proteinuria ≥1.5 mg/mg (≥2 mg/mg for Class V) and estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m2. Patients who completed AURORA 1 were eligible to enroll in AURORA 2 on the same blinded treatment of voclosporin or placebo in combination with MMF (target dose 2 g/day) and low-dose oral steroids. Per-protocol steroid use in AURORA 1 required a rapid taper from a starting dose of 20–25 mg/day to a target of ≤2.5 mg/day by Week 16. The final dose of steroids in AURORA 1 was the initial starting dose in AURORA 2; the dose could then be adjusted further at the discretion of the study investigator. AURORA 2 was not designed nor powered to address the impact of voclosporin on oral steroid dose.

Results In total, 116 patients in the voclosporin arm and 100 patients in the control arm enrolled in AURORA 2. The efficacy observed in patients treated with voclosporin in AURORA 1 was maintained throughout AURORA 2 as indicated by the greater Least Square (LS) mean reductions in UPCR from baseline in the voclosporin arm vs. control arm at all time points (Figure 1A). The overall exposure to oral



Analysis of AURORA 2 patients includes data from pre-treatment baseline of AURORA 1, 12 months in AURORA 1, and up to 25 months of follow-up in AURORA 2 (including 4-week post-treatment visit). CI, confidence interval; eGFR, estimated glomerular filtration rate; FUP, follow-up visit (occurred 4 weeks post-discontinuation of study drug); LS Mean, least squares mean; UPCR, urine protein creatinine ratio.

Abstract S06.2 Figure 1 A) UPCR and B) eGFR over time

Abstract S06.2 Table 1 Oral steroid use

	Voclosporin	Control
AURORA 2 Baseline (Month 12[a]) n (%)	n=116	n=100
>2.5 mg/day	14 (12.1)	15 (15.0)
≤2.5 mg/day	102 (87.9)	85 (85.0)
Month 24, n (%)	n=111	n=88
>2.5 mg/day	22 (19.8)	14 (15.9)
≤2.5 mg/day	89 (80.2)	74 (84.1)
Month 36, n (%)	n=101	n=85
>2.5 mg/day	24 (23.8)	19 (22.4)
≤2.5 mg/day	77 (76.2)	66 (77.6)

[a]Analysis of AURORA 2 patients includes 12-month data from AURORA 1 (AURORA 2 baseline) and 24 months of follow-up in AURORA 2. Values are number (percentage) calculated out of number of patients in study at time point.

steroids during the study was similar for both treatment arms; over three years of treatment, the majority of patients were on steroid doses ≤2.5 mg/day (Table 1). There were no new or unexpected safety signals detected in patients who continued on voclosporin treatment compared to control-treated patients with similar rates of serious adverse events in the voclosporin (18.1%) and control arms (23.0%). There were no deaths in the voclosporin arm during AURORA 2; four deaths were reported in the control arm (pulmonary embolism [n=1], coronavirus infection [n=3]). Mean eGFR remained stable throughout the study (Figure 1B).

Conclusions Voclosporin was safe and well-tolerated over three years of treatment with a similar safety profile to control and no unexpected safety signals detected. Further, the significant reductions in proteinuria initially achieved in AURORA 1 were maintained in AURORA 2 even in the absence of traditional high-dose steroids. These data provide evidence of a long-term treatment benefit of voclosporin in patients with lupus nephritis and also support the use of lower doses of steroids in the treatment of this disease.

S06.3 EVALUATION OF PREDICTIVE FACTORS OF WORSE PROGNOSIS IN LUPUS NEPHRITIS: FOCUS ON NEW PATHOGENETIC PATHWAYS

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Purpose Cytokine dysregulation plays an important role in the pathogenesis of lupus nephritis (LN). IL-17/IL-23 axis seems to have an important influence in the development of LN. The aim of this study is to evaluate the strongest prognostic factors in a cohort of patient with LN focusing on of the impact of IL-17/IL 23 axis as emerging pathogenetic pathway on renal outcome.[1,2]

Methods 91 patients with active LN (76 females and 15 males; mean age at study entry± SD, 44.1 ± 12.1, mean follow-up in months ± SD, 78.5 ± 50.1) at disease onset or at disease flare were enrolled. Laboratory, immunological and disease activity data were collected at baseline and at 6(T6),12 (T12),24(T24) months and at the last follow-up(FU). 84 renal biopsies were evaluated according to ISN/RPS classification, assessing the activity and chronicity indices and the active interstitial infiltrate using the BANFF score system. Baseline IL-17 and IL-23 serum levels were assessed by ELISA in 37 patients.

Results among the 84 renal biopsies evaluated 77% belonged to class III and IV according to ISN/RPS; 41,8% of patients had a renal active interstitial infiltrate (>5%). Regardless any significative difference in the IL -17 serum levels between patients with worse versus favourable nephritis course, patients with higher IL-17 serum levels at the baseline showed higher levels of renal interstitial infiltrate and a worse renal outcome overall. Finally, at univariate and multivariate analysis for each renal outcome considered, active interstitial infiltrate (>5%) at renal biopsy and the presence of at least one antiphospholipid antibodies positivity (APL+) were associated with worse renal outcomes. In particular active inflammatory interstitial infiltrate was associated to worse renal outcome in terms of not reaching early remission in both univariate analysis (p<0,01) and multivariate analysis (OR 0.12 (0.04–0.37)), while it was associated to chronic damage (p= 0,01), no persistent remission (p= 0,02), persistent proteinuria (p <0,01), and renal flare (p<0,001) in the univariate analysis. APL+ was associated to worse renal outcome in terms of early remission in both univariate analysis (p= 0,03) and multivariate analysis (OR 0.36(0.11–1.37)) as well as to chronic renal damage in univariate analysis (p= 0,04) and multivariate analysis (OR 0.77 (0.39–15.16)), while it was associated to persistent remission (p= 0,01) and persistent proteinuria (p= 0,01) in the univariate analysis. Higher IL-23 serum level was associated with persistent proteinuria (p<0,01) and chronic renal damage (p=0.05).

Conclusion interstitial inflammatory infiltrate and APL+ represent in our study the strongest predictors of worse renal outcome. A higher IL-23 serum level was found to be a negative prognostic factor suggesting a possible role of IL-17/IL 23 axis as a biomarker of a more aggressive renal disease.

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Thursday 06 October 2022 from 08:00 to 10:00

S09 SLE EPIDEMIOLOGY AND STUDIES OF SUBGROUPS

S09.1 INCIDENCE AND PREVALENCE OF SYSTEMIC LUPUS ERYTHEMATOSUS IN A LARGE POPULATION-BASED STUDY IN NORTHEASTERN ITALY, BETWEEN 2012 AND 2020

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Objectives Incidence and prevalence of SLE widely vary across different countries, being influenced by study design, population demographics, and ethnicity. Four studies evaluated the epidemiology of SLE in Italy: they covered a short period of time (4 year at most), two of them were published more than fifteen years ago, and they all involved a small number of participants (112,365, 346,000, 71,204, and 25,885 individuals as the general population screened, respectively).[1–4] We aimed at estimating the incidence and prevalence of SLE in northeastern Italy over the period 2012–2020.

Methods A retrospective population-based study was conducted in Veneto Region using the Population Registry, an administrative health database where all residents are recorded (about 4.9 million people). The population registry was linked with healthcare co-payments exemptions, hospital discharge records, and mortality records. SLE was defined by any hospital diagnosis of SLE (ICD-9-CM 710.0) or a healthcare copayment exemption for SLE (national registry code 028). Standardized incidence and prevalence were estimated per 100,000 people in the period 2012–2020, stratified by age, gender, and year.