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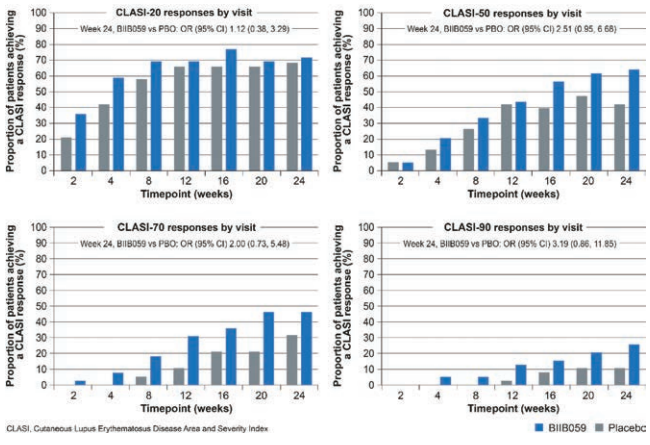
Background: SLE is a heterogeneous disease with diverse clinical presentations, and up to 70–80% of patients develop skin manifestations.[1–3] In SLE, plasmacytoid dendritic cells (pDCs), a major source of Type I interferon (IFN), accumulate in the skin.[4] Treatment with BIIB059, a humanized monoclonal antibody targeting blood dendritic cell antigen 2 (BDCA2) that is expressed on pDCs, leads to rapid internalization of BDCA2 from the surfaces of pDCs and inhibits the production of Type I IFNs, pro-inflammatory cytokines, and chemokines.[5] Part A of the randomized, two-part, Phase 2 LILAC study (NCT02847598) enrolled participants with SLE and active skin and joint disease. The primary endpoint was met, with a greater reduction in total active joint count at Week 24 in the BIIB059 treatment group vs placebo (PBO), and more participants achieved a ≥50% improvement from baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity (CLASI-A) score with BIIB059 vs PBO.[6]
Objectives: To further evaluate the effect of BIIB059 vs PBO in reducing skin disease activity, as measured by various CLASI-A response thresholds.
Methods: Adults with an SLE diagnosis according to the revised ACR 1997 SLE classification criteria, with ≥4 tender and ≥4 swollen joints (28-joint assessment), active skin disease (as defined by the SLE Disease Activity Index 2000 [SLEDAI-2K]), and positive anti-nuclear antibodies and/or anti-double-stranded DNA antibodies, were enrolled. Participants were randomized to receive BIIB059 450 mg or PBO, administered subcutaneously every 4 weeks with an additional dose at Week 2. Improvements in skin disease were assessed in participants with baseline CLASI-A score ≥8. The proportion of participants achieving a ≥7-point reduction from baseline in CLASI-A score was assessed at Week 24, and CLASI-20, -50, -70, and -90 responses were assessed over time. Achievement of CLASI-A scores of 0–1 was also assessed at Week 24. These analyses used non-responder imputation with logistic regression, without correction for multiplicity. The proportions of participants achieving CLASI-A scores of 0–3 and with resolution of SLEDAI-2K skin rash at Week 24 were evaluated *ad hoc* in the same population. Non-responder imputation was applied to visits post treatment failure and treatment discontinuation. Improvement from baseline in British Isles Lupus Assessment Group index (BILAG-2004) A or B mucocutaneous domains was similarly assessed at Week 24. P-values were calculated based on the odds ratios (ORs) for BIIB059 compared with PBO.
Results: At Week 24, a significantly greater proportion of participants receiving BIIB059 (n=39) vs PBO (n=38) had a ≥7-point reduction in CLASI-A score from baseline to Week 24 (56.4% vs 34.2%, OR [95% confidence interval {CI}] 2.71 [1.03, 7.17], P=0.044). Numerically greater proportions of participants receiving BIIB059 vs PBO achieved CLASI-50, CLASI-70, or CLASI-90 responses (Figure 1). Similarly, the proportion of participants who achieved CLASI-A scores of 0–1 was greater in the BIIB059 group vs PBO (25.6% vs 13.2%), as was the proportion who achieved CLASI-A scores of 0–3 (48.7% vs 28.9%). A greater proportion of BIIB059- vs PBO-treated participants had resolution of SLEDAI-2K skin rash at Week 24 (28.6% vs 10.7%), with similar findings seen in the BILAG-2004 mucocutaneous domain.

Figure. Patients achieving CLASI-20, -50, -70, and -90 responses by visit



Conclusion: Numerically greater reductions in skin disease activity were consistently observed with BIIB059 treatment vs PBO in participants with SLE and active skin disease, supporting a potential benefit of BIIB059 treatment for skin manifestations in SLE.

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POS0185 BELIMUMAB DISRUPTS MEMORY B-CELL TRAFFICKING IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Belimumab (BEL), a recombinant human monoclonal antibody directed against B-cell activating factor (BAFF), is the first approved biological agent for patients with active systemic lupus erythematosus (SLE) and lupus nephritis (LN).[1] BEL inhibits primary humoral immune responses by depleting naïve B cells that are dependent on BAFF for their survival while secondary humoral immune responses by memory B cells (MBCs) remain intact. Indeed, some studies reported an increase of circulating MBCs following neutralisation of BAFF.[2-4] So far, these effects of BEL on the MBC compartment in SLE patients have not been investigated.
Objectives: This study aimed to establish the dynamics of circulating MBCs in patients with SLE treated with BEL and to perform an in-depth analysis of the impact of BEL on the MBC compartment.
Methods: First, a retrospective meta-analysis was performed by pooling individual patient MBC flow cytometry data from 1245 patients with SLE treated with BEL 10 mg/kg IV or placebo (PBO) from four randomised clinical trials (NCT00071487, NCT00410384 [BLISS-76],[3] NCT01632241 [EMBRACE],[5] NCT01649765 [PLUTO][6]). Second, extensive B-cell subset phenotyping was performed prospectively by employing high-sensitivity flow cytometry (HSFC) based on EuroFlow protocols[7] in patients with active SLE (from the BLISS-BELIEVE trial [NCT03312907])[8] and with severe SLE/LN (from the SynBioSe-2 trial [NCT03747159])[9] treated with BEL. Additionally, in-depth characterisation of surging MBCs in circulation was performed by single-cell RNA sequencing (scRNA-seq).
Results: By comparing BEL-treated with PBO-treated patients with SLE, a substantial increase in circulating MBC counts was established 4 weeks after BEL initiation, gradually returning to baseline by Week 52. The increase of MBCs was most prominent in BEL-treated patients with higher SLE disease activity (SLE

Disease Activity Index >9), serologically active patients (dsDNA positive and/or low complement levels) and with younger age (below 18 years). HSFC established that the increase was non-specific and observed in a broad range of MBC subclasses peaking as early as 2 weeks after BEL initiation. Subsequent scRNA-seq analysis of the emerging MBCs revealed a non-proliferating phenotype with a prominent decrease in activation status. In these circulating MBCs, a large amount of migration and adhesion genes were downregulated suggesting that the accumulation of MBCs following BEL treatment was related to their impaired cell-cell adhesion, disrupting cell-trafficking and preventing extravasation.

Conclusion: After initiation of BEL treatment, a substantial increase of circulating MBCs was firmly established and was most notable in patients with severe, serologically active SLE/LN. The surge of circulating MBCs appeared to be associated with disrupted lymphocyte trafficking of MBCs, thereby suggesting a new potential therapeutic mechanism of BEL on MBCs in SLE. These findings have important implications to our understanding and consequent improvement of B-cell targeted treatment strategies in patients with active SLE and LN, as MBC accumulation in circulation might allow for more efficient targeting of the B-cell compartment.

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POS0186 VOCLOSPORIN FOR LUPUS NEPHRITIS: RESULTS OF THE TWO-YEAR AURORA 2 CONTINUATION STUDY

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Background: Voclosporin (VCS), a novel calcineurin inhibitor, was approved in the US in January 2021 for the treatment of adult patients with active lupus nephritis (LN) in combination with background immunosuppressive therapy. The Phase 3 AURORA 1 study showed that the addition of VCS to mycophenolate mofetil (MMF) and low-dose steroids in patients with LN significantly increased rates of complete renal response at 52 weeks.

Objectives: Here we report the results of the completed continuation study, AURORA 2, which assessed the long-term safety and tolerability of VCS compared to placebo in patients with LN receiving treatment for an additional 24 months following completion of the AURORA 1 study

Methods: Key inclusion criteria for the parent AURORA 1 study included a diagnosis of biopsy-proven active LN (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 m^2. Patients who completed AURORA 1 and who elected and were eligible to enter AURORA 2 continued on the same blinded therapy as at the end of AURORA 1 (either VCS or placebo twice daily in combination with MMF and low-dose steroids). Safety and tolerability were monitored, and eGFR, serum creatinine (SCr), and urine protein creatinine ratio (UPCR) were also assessed.

Results: In total, 116 and 100 patients in the VCS and control arms enrolled in AURORA 2, with 92 (79.3%) and 73 (73.0%) patients in each respective arm receiving treatment to the end of AURORA 2. There were no unexpected safety signals in the VCS arm compared to control, with similar rates of serious adverse events reported in both arms (VCS [18.1%] vs. control [23.0%]; Table 1). Eight patients in each arm experienced serious adverse events of infection; serious coronavirus infections were observed in 2 patients in the voclosporin arm and 5 patients in the control arm. There were 4 and 2 adverse events by preferred term of renal impairment reported in the VCS and control arms, respectively, none of which were considered serious, and no reports of acute kidney injury by preferred term in either arm. There were no deaths in the VCS arm during AURORA 2; four deaths were reported in the control arm (pulmonary embolism [n=1], coronavirus infection [n=3]). Mean eGFR and SCr levels remained stable through the end of AURORA 2. The difference between the VCS and control arms in LS mean change from baseline in eGFR was 2.7 mL/min/1.73 m^2 at 4 weeks following study drug discontinuation (Figure 1). The mean reductions in UPCR observed in patients treated with VCS in AURORA 1 were maintained in AURORA 2 with no increase in UPCR noted at the follow-up visit 4 weeks after study drug discontinuation.

Table 1. Overall Summary of Adverse Events

	Control (n=100)	Voclosporin (n=116)
	n (%)	n (%)
Any AE	80 (80.0)	100 (86.2)
Renal Impairment	2 (2.0)	4 (3.4)
Acute Kidney Injury	0	0
Treatment-related AE	21 (21.0)	28 (24.1)
Serious AE	23 (23.0)	21 (18.1)
Serious Treatment-related AE	2 (2.0)	1 (0.9)
AE Leading to Study Drug Discontinuation	17 (17.0)	11 (9.5)
Death	4 (4.0)	0
Treatment-related Death	0	0

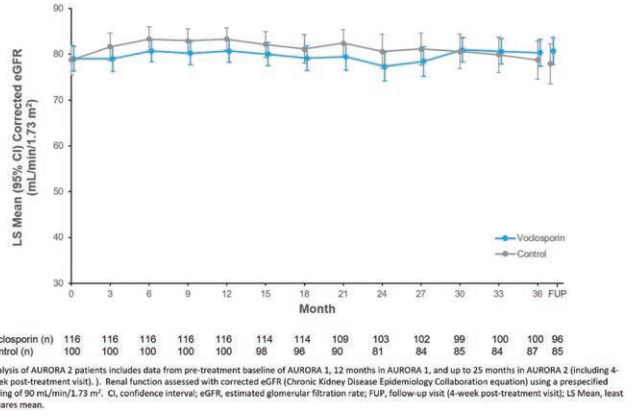

Figure 1. LS Mean eGFR over Time

Conclusion: Voclosporin was well-tolerated over 3 years of treatment with no unexpected safety signals detected. Further, eGFR remained stable throughout the study period, and the significant and meaningful reductions in proteinuria achieved in AURORA 1 were maintained. These data provide evidence of a long-term treatment benefit of VCS in patients with LN.

Includes adverse events starting on or after the first dose of study drug in AURORA 2 up to 30 days after the last dose and all events of death reported during study follow-up. Adverse events were aggregated by System Organ Class and Preferred Term and coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. AE, adverse event.

Disclosure of Interests: Amit Saxena Speakers bureau: Aurinia Pharmaceuticals Inc., Consultant of: Aurinia Pharmaceuticals Inc., Y.K. Onno Teng Consultant of: Aurinia Pharmaceuticals Inc., Chris Collins Shareholder of: Aurinia Pharmaceuticals, Employee of: Aurinia Pharmaceuticals, Nicole England Shareholder of: Aurinia Pharmaceuticals, Employee of: Aurinia Pharmaceuticals, Henry Leher Shareholder of: Aurinia Pharmaceuticals, Employee of: Aurinia Pharmaceuticals

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