Figure 1. Figure showing the ROC curve for MISA and MISS questionnaires for MTX intolerance (A), Bar diagram showing the prevalence of various symptoms of intolerance in 414 RA patients (B), and Box-and-whiskers plot showing the duration of unpleasant symptoms (C).

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SLE, Sjögren's and APS – treatment

POS0680

BELIMUMAB ADD-ON THERAPY MOBILISES MEMORY B CELLS INTO THE CIRCULATION OF PATIENTS WITH SLE

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Background: Belimumab (BLM), a recombinant human monoclonal antibody directed against B-cell activating factor (BAFF), is the first approved biological agent for patients with active severe systemic lupus erythematosus (SLE) and lupus nephritis (LN). There is clinical evidence that combining BLM with B cell depleting therapy can ameliorate disease activity in severe, refractory SLE patients¹. Although BLM is a B cell directed therapy and has been shown to significantly decrease total B cells, flow cytometry observations suggest a rapid increase of circulating memory B cells (MBC)².

Objectives: To investigate dynamics of B-cell subsets in SLE patients treated with or without BLM, with a focus on assessing MBC characteristics.

Methods: Extensive B cell subset phenotyping was performed by high-sensitivity (HS) flow cytometry (acquisition of 10⁷ leukocytes; per EuroFlow protocols³) on samples from active LN or SLE patients with major organ involvement treated with standard of care (SOC) consisting of high dose steroids and mycophenolate mofetil combined with or without the addition of BLM. MBC gene expression profiles were characterized with single-cell RNA and V(D)J sequencing (ScRNA-SEQ).

Results: By employing HS flowcytometry, we established that the absolute increase in circulating MBC in SLE and LN patients was significant for patients who initiated BLM (Figure 1). The increase was observed in a broad range of MBC subsets (Unswitched, IgG1+, IgG2+, IgA1+, IgA2+) at 2 and 4 weeks following initiation of BLM treatment. This rise in MBC could hypothetically be attributed to either proliferation of blood MBC, BLM induced migration of tissue-resident MBCs or BLM related retention of tissue-destined MBC in the blood. ScRNA-SEQ analysis of cell cycle gene-expression was performed and established in both groups a non-proliferating phenotype [in approximately ~94%] of MBC post-treatment, including absence of MKI67 as active proliferation marker. Clonal diversity analysis comparing week 2 with baseline revealed an unexpected decrease of the largest MBC clones in BLM, whereas no change in clonality was observed with SOC alone. Together these data indicate that proliferation is unlikely to be responsible for the observed increase in MBC by BLM. Furthermore, a clear difference was found in gene-expression levels between both treatment groups:

Figure 1. Change in pre-germinal center and memory B cell counts from baseline to week 4 of patients with SLE or LN treated with SOC (n=8) or SOC+BLM (n=11).

BLM was responsible for the upregulation of 72 vs 10 genes in SOC, likewise 162 vs 32 genes were downregulated. Most importantly, a significant downregulation of the migration genes SELL (CD62L), CCR7, ITGB1, RAC2 and ICAM2, were specifically seen in BLM treated patients. This may reflect disrupted lymphocyte trafficking, preventing MBCs from transmigration from the blood into tissue owing to reduced migration molecules, or preventing MBCs from being retained at the tissue level owing to reduction in tissue adhesion proteins.

Conclusion: The addition of BLM to SOC significantly increases MBCs in patients with SLE independently of proliferation, accompanied by a strong modulation of gene expression, including reduced expression of migration markers pointing towards disrupted lymphocyte trafficking. These data may have important implications for improving treatment strategies in patients with LN or severe SLE, as a deeper depletion of autoreactive MBCs could be established by adding B-cell-depleting therapy after the initiation of BLM.

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POS0681

VOCLOSPORIN FOR LUPUS NEPHRITIS: INTERIM ANALYSIS OF THE AURORA 2 EXTENSION STUDY

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Background: Voclosporin, a novel calcineurin inhibitor (CNI), has been tested successfully in two pivotal trials in adult patients with lupus nephritis.

Previously reported results from the Phase 3 AURORA 1 study and the Phase 2 AURA-LV study showed that compared with mycophenolate mofetil (MMF) and low-dose steroids alone, the addition of voclosporin significantly increased the renal response rate and reduced proteinuria, as measured by urine protein creatinine ratio (UPCR), in patients with lupus nephritis (LN) at approximately one year of treatment (48 weeks in AURA-LV and 52 weeks in AURORA 1).

Objectives: Patients that completed one year of treatment in the AURORA 1 study were eligible to enroll into the two-year, blinded, controlled extension study, AURORA 2. Here we report the first interim analysis of the ongoing AURORA 2 study.

Methods: Patients completing AURORA 1 were eligible to continue the same randomized treatment of voclosporin (23.7mg BID) or placebo, in combination with MMF (1 g BID) and low-dose oral steroids in the AURORA 2 extension. This interim analysis evaluated UPCR and estimated glomerular filtration rate (eGFR) in patients with up to two years of total treatment: one year from AURORA 1 and up to one year in AURORA 2.

Results: 116 patients in the voclosporin arm and 100 patients in the control arm enrolled in the extension study, of which 73 patients in the voclosporin arm and 51 patients in the control arm had received two years of treatment at the time of this interim analysis. Mean UPCR at pre-treatment (AURORA 1) baseline was 3.94 mg/mg in the voclosporin arm (n=116) and 3.87 mg/mg in the control arm (n=100). The LS mean change in UPCR from pre-treatment baseline to year two was -3.1 mg/mg for the voclosporin arm (n=73) and -2.1 mg/mg for control arm (n=51; Table 1). Mean eGFR at pre-treatment (AURORA 1) baseline was 79.6 mL/min for the voclosporin arm (n=116) and 78.9 mL/min for the control arm (n=100) and at year two, was 79.0 mL/min for the voclosporin arm (n=73) and 82.9 mL/min for the control arm (n=51). There was a small early decrease in mean eGFR in the first four weeks of treatment (in AURORA 1) after which eGFR remained stable throughout year one and year two. Additionally, there

were no unexpected new AEs observed in patients who continued with voclosporin treatment compared to control-treated patients for more than one year.

Table 1. UPCR

	Control (n=100)		Voclosporin (n=116)		Treatment Comparison of Voclosporin to Control	
	n	UPCR (mg/mg)	n	UPCR (mg/mg)	UPCR (mg/mg)	p-value
Pre-treatment baseline, mean	100	3.87	116	3.94	NC	NC
Change from pre-treatment baseline, LS mean						
Year 1	100	-2.4	116	-3.0	-0.6	0.0080
Year 2	51	-2.1	73	-3.1	-1.0	0.0004

LS, least squares; NC, not calculated; UPCR, urine protein creatinine ratio. Mixed effects model for repeated measures (MMRM) analysis of LS mean change from pre-treatment baseline for UPCR included terms for baseline covariate, treatment, visit and treatment by visit interaction. Integrated results include data from pre-treatment baseline of AURORA 1, the one-year treatment period in AURORA 1 and up to a one-year treatment period in AURORA 2.

Conclusion: Patients in the voclosporin treatment arm maintained meaningful reductions in proteinuria with no change in mean eGFR at two years of treatment. Additional AURORA 2 efficacy and safety data will be provided at the conclusion of the study.

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POS0682

RETROSPECTIVE ANALYSIS OF PREGNANCY OUTCOMES IN PATIENTS WITH OBSTETRIC ANTIPHOSPHOLIPID SYNDROME (OAPS), NON-CRITERIA OAPS (NC-OAPS) AND ANTIPHOSPHOLIPID CARRIERS

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Background: Antiphospholipid (aPL) antibodies are considered in obstetric morbidity even when Sydney criteria for OAPS are not met. Classification and treatment of NC-OAPS patients and aPL carriers during pregnancy are still debated.

Objectives: To increase knowledge, we evaluated and compared aPL serum profiles, exposure to antithrombotic therapies and pregnancy outcomes in OAPS, NC-OAPS and aPL carrier patients, accessing to our centre.

Methods: A retrospective observational study was conducted on pregnant outpatients from January 2003 to April 2020. According to Sydney revised classification criteria, we considered lupus anticoagulant (LA), IgM and IgG anti-cardiolipin antibodies (aCL), IgM and IgG anti-beta2 glycoprotein I antibodies (aβ2-GPI), to stratify aPL risk profiles [Ref]. In each pregnancy, after case stratification into high (≥ 2 aPL or LA serum positivity) versus low (single aPL positivity) risk profile, we evaluated antithrombotic treatment strategy and subsequent pregnancy outcomes as live-births, spontaneous abortions (SA) or foetal losses.

Results: A total of 78 pregnancies were followed: 17 in OAPS, 9 in NC-OAPS and 52 in aPL carrier patients. Rheumatic diseases (RD) coexisted predominantly in carriers (73.1%), mainly systemic lupus erythematosus (57.9%). As presented in Table 1, in OAPS and aPL plus RD carrier groups the association of acetyl-salicylic acid (ASA - mean dose 100 mg q.d.) and low-molecular weight heparin (LMWH - mean dose 4000 UI q.d.) showed a better rate of positive outcomes (97.8% of pregnancies) in high aPL risk profile, compared to monotherapy, especially with LA or triple aPL positivity. Conversely, negative outcomes occurred mostly with triple aPL positivity in the first group and double aPL in the second, despite therapy approaches. No significant data were obtained in NC-OAPS group, due to its paucity, though adverse outcomes were observed with monotherapy both in high and low risk profiles. Except aPL carriers with RD, in all other low risk subgroups, a prevalence of negative outcomes occurred using ASA alone, without statistical significance (OR 0; p= 0.45). Similarly, considering the whole population, the use of a mono or a combination therapy in high risk subgroups had not a significant correlation with pregnancy outcomes (OR 1.79; 95%CI 0.31-10.15; p= 0.50).

Conclusion: In our study, negative pregnancy outcomes were sporadic, occurring mostly with ≥ 2 aPL positivity. Combination treatment showed better results overall in high aPL risk profile patients, both in OAPS and NC-OAPS or aPL carriers. Though no significant correlation between outcomes and treatments were

found, we hinted how aPL-based risk stratification may be useful in adopting personalised therapies to prevent obstetric failures.

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Table 1. Population groups, aPL risk profiles, antithrombotic therapies and pregnancy outcomes.

Population group	aPL risk profile	Type/n° of aPL	Therapy (n° of pregnancies)	Pregnancy outcomes
OAPS	High	LA	ASA (1)	1 live-birth
		2 aPL	ASA + LMWH (1)	1 live-birth
		3 aPL	ASA + LMWH (3)	3 live-births
	Low	1 aPL	ASA + LMWH (9)	7 live-births
				2 foetal losses
			ASA (2)	1 live-birth
NC-OAPS	High	LA	ASA + LMWH (1)	1 foetal loss
				1 live-birth
		2 aPL	ASA (1)	1 live-birth
	Low	3 aPL	LMWH (1)	1 SA
			ASA (6)	5 live-births
		1 aPL		1 SA
aPL carriers without RD	High	LA	ASA + LMWH (1)	1 live-birth
				1 live-birth
		2 aPL	LMWH (1)	1 live-birth
	Low	3 aPL	ASA (1)	1 live-birth
			LMWH (2)	2 live-births
		1 aPL	ASA (5)	1 live-birth
aPL carriers with RD	High	LA	ASA + LMWH (3)	3 live-births
			ASA (5)	4 live-births
		2 aPL	ASA (4)	1 foetal loss
	Low	3 aPL	ASA + LMWH (7)	3 live-birth
				1 foetal loss
		1 aPL	ASA (6)	6 live-births
	High	LA	ASA (6)	1 SA
			ASA + LMWH (4)	6 live-births
		2 aPL		2 live-births
	Low	3 aPL	LMWH (2)	1 SA
			ASA + LMWH (5)	1 foetal loss
		1 aPL	ASA (8)	2 live-births
	Low		ASA + LMWH (3)	5 live-births
				8 live-births
				3 live-births

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POS0683

NOVEL STRINGENT OUTCOME MEASURES APPLIED TO THE PHASE 2 AND 3 ANIFROLUMAB TRIALS

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