For every 100 units increase in Elastase-DNA complexes there is an 7.3% decrease (95% CI 4.4-10.8) in eGFR (p=<.0001)

For every 100 units increase in HMGB1-DNA complexes there is an 7.6% decrease (95% CI 3.4-11.8) in eGFR (p=0.0005)



Abstract 1117 Figure 2 Linear regression analysis showing a linear relationship between the amount of Elastase-DNA and HMGB1-DNA complexes and the decline in kidney function in the following 2 years. *Adjusted to age, sex, ethnicity and immunosuppressive therapy received in the prior 3 months

Abstract 1117 Table	1 Logistic Regression analysis*. Higher
baseline levels of NET	complexes increase the odds of non-response
to therapy and severe	renal impairment in the following 2 years
after the LN flare (N=	109)

	12 months after renal flare		24 months after renal flare		
Variables (at baseline, ±3 months from the LN flare)	Odds Ratio (95% Cl)	P value	Odds Ratio (95% CI)	P value	
Failure to achieve comple	ete renal response				
Elastase-DNA	1.68 (0.98-2.88)	0.056	2.00 (1.00-3.79)	0.05	
HMGB1-DNA	2.17 (1.10-4.26)	0.02	1.93 (1.04-3.60)	0.03	
24-hour proteinuria	2.03 (0.95-4.32)	0.06	1.11 (0.55-2.24)	0.75	
Anti dsDNA ab	1.71 (0.79-3.65)	0.16	1.55 (0.75-3.21)	0.23	
C3	0.77 (0.46-1.27)	0.31	0.71 (0.43-1.17)	0.18	
C4	0.96 (0.58-1.79)	0.88	0.87 (0.50-1.49)	0.62	
Presence of severe renal impairment (eGFR≤30ml/min)					
Elastase-DNA	1.34 (0.96-1.87)	0.08	1.68 (1.15-2.45)	0.006	
HMGB1-DNA	1.77 (0.90-3.45)	0.09	1.86 (1.03-2.38)	0.03	
Proteinuria	4.00 (1.25-12.87)	0.02	1.96 (0.75-5.06)	0.16	
Anti dsDNA ab	1.20 (0.41-3.49)	0.73	2.32 (0.96-5.51)	0.056	
C3	1.93 (0.59-3.41)	0.53	0.76 (0.63-1.61)	0.48	
C4	1.52 (0.77-2.97)	0.22	0.98 (0.45-2.09)	0.96	

* The Logistic Regression analysis for each of the variables of interest was adjusted for ag sex, ethnicity and immunosuppressive therapy received in the prior 3 months.

to inactive patients. Patients with ALN (36.7%) had significantly higher levels of NET complexes compared to active SLE without LN. Furthermore, patients with proliferative LN had higher levels of NET complexes compared to non-proliferative LN (figure 1).

The LN cohort included 109 ALN patients. The median (IQR) age was 29 (23-41) years, 84% were women, and disease duration was 6.4 (0.8-10.5) years. 37.9% were Caucasian, 22.2% Black and 17.5% Asian, the baseline eGFR was 112 (97-127) ml/min. 77.9% had a kidney biopsy at the time of the LN flare, of whom 55.9% had a proliferative or mixed class, 17.4% class V, and 4.5% class I or II. 39.4% and 50.5% of the ALN patients achieved CR at 12 and 24

months, respectively and 11% had an eGFR \leq 30ml/min after 24 months.

Similar to the results from the exploratory cohort, proliferative LN had higher levels of NET complexes compared to non-proliferative LN patients (Elastase-DNA: 111.7 vs 25.9, p=0.0003; HMGB1-DNA: 85.2 vs 25.4, p=0.002, proliferative vs non-proliferative, respectively). Patients with higher baseline levels of NET complexes had higher odds of not achieving CR and of having severe renal impairment after 24 months of the flare. NET complexes outperformed conventional biomarkers (table 1). There was a linear relationship between the amount of baseline Elastase-DNA and HMGB1-DNA complexes and the decline in renal function in the subsequent 24 months (figure 2).

Conclusions Elastase-DNA and HMGB1-DNA complexes predicted renal outcomes, including response to therapy and decline in kidney function at 2 years after the LN flare.

1201 IMPACT STUDY: PRELIMINARY RESULTS OF A TRIAL WITH A BIOLOGIC TO PREVENT PREECLAMPSIA IN WOMEN WITH ANTIPHOSPHOLIPID SYNDROME

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Background Pregnant women with antiphospholipid antibodies and/or lupus have higher rates of adverse pregnancy outcomes (APOs), such as fetal loss and preterm birth due to severe preeclampsia (PE) or placental insufficiency (PI). The presence of lupus anticoagulant (LAC) is the strongest predictor of an APO. At present, there is no effective treatment for women with these high-risk pregnancies, but in an animal model that mimics this human condition we found that TNF- α was a critical downstream effector of abnormal placental development and fetal damage, and that TNF- α blockade normalized placentation and spiral artery remodeling, and rescued pregnancies. We sought to determine whether TNF- α blockade during pregnancy, added to a regimen of heparin and low dose aspirin, reduces the rate of APOs in women with clinical APS and LAC. Methods The IMPACT Study (IMProve Pregnancy in APS with Certolizumab Therapy) is an open label single-stage Phase II trial to evaluate the effect of certolizumab, a TNF- α inhibitor that does not cross the placenta and has been shown to be well tolerated in pregnancy, to reduce the risk of adverse outcomes in this population. Patients with APS and LAC are referred to IMPACT by their physicians, consented and screened remotely by a study investigator, and medication is sent to the patient. They are treated with certolizumab from gestational week 8 through 28. Investigators contact patients every 2 weeks and receive medical reports and research blood samples monthly. The primary outcome is a composite of two APOs associated with poor placentation: fetal death >10 WG or severe preeclampsia/placental insufficiency requiring delivery prior to 34 weeks gestation. The target sample size is 45 evaluable subjects. We hypothesize that the rate of the primary outcome in these pregnancies will be reduced from ~40% based on historical data to 20% with certolizumab.

Results Since May 2017 and despite the COVID-19 pandemic, we have enrolled 41 patients from ten states and 1 Canadian province. Characteristics: 56% previous PE or PI <34 weeks requiring delivery, 83% previous fetal death >10 weeks; 61% thrombosis and/or stroke and 24% SLE in addition to APS. During the trial, no new clinical manifestations of SLE have been observed in participants who did not carry the SLE diagnosis. There were no instances of new anti-DNA antibodies or increases in autoantibody titres in those patients who were anti-DNA antibody positive. ACL or anti- β 2GPI antibody titres did not change during the trial. There have been no serious adverse events attributable to the study medication.

Conclusion We are successfully using a "rare disease study" approach to conduct the first trial of a biologic therapy to prevent pregnancy complications in women with APS and LAC. Certolizumab appears to be safe in this small trial. Certolizumab appears to be safe so far in this small trial. IMPACT must be completed before we can draw any conclusions about efficacy, and its results must be confirmed in a future study.

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Lay Summary Pregnancies in patients with antiphospholipid syndrome who have a lupus anticoagulant in their blood have a high likelihood of ending in fetal death or very premature delivery because of poor placental development and preeclampsia. At present, there is no effective treatment for women with these high-risk pregnancies, but our work in an animal model that mimics this human condition shows that blockade of TNF-a, a pivotal mediator of inflammation, prevents adverse outcomes. Our study will determine whether treatment during pregnancy with certolizumab, a TNF-a inhibitor that does not cross the placenta, reduces the rate of poor pregnancy outcomes in women with clinical antiphospholipid syndrome; and, if successful, it will provide a new approach to protecting pregnancies in women with antiphospholipid syndrome and a rationale for trials of TNF- α blockade in women with other conditions, like SLE, who are at risk for preeclampsia or placental insufficiency.

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1202 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. 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 \pm III/IV), proteinuria \geq 1.5 mg/mg (\geq 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 enter AURORA 2 to continue 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. 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 two 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 m² 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.

Conclusion Voclosporin was well-tolerated over 3 years of treatment with no unexpected safety signals detected. Further,