groups (groups 2-4) with decreased glomerular and tubular damage scores (Figure 1G). Most importantly, frequencies of CD8⁺CD25⁺FoxP3⁺ regulatory T cells and CD19⁺CD5⁺CD1d^{high} regulatory B cells were significantly higher in MIC-treated (groups 2-4) compared to control animals of group 1, whereas double negative T cells were markedly reduced (Figure 1H).

Conclusion: MIC therapy inhibits progression of active lupus nephritis. Interestingly, preemptive MIC therapy was even able to prevent onset of disease with no significant disease activity at completion of the study. In accordance with our previous pre-clinical EAE experiments (1) and a first in-human clinical trial in living-donor kidney transplantation (TOL-1 study), MIC therapy was able to induce an in-vivo induction of regulatory cell subsets. This clinically applicable cell therapeutic approach may control lupus nephritis by specifically silencing deleterious autoimmune responses.

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OP0041

MAINTENANCE OF EFFICACY AND SAFETY AND REDUCTION OF BILAG FLARES WITH USTEKINUMAB, AN INTERLEUKIN-12/23 INHIBITOR, IN PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): 1-YEAR RESULTS OF A PHASE 2, RANDOMIZED PLACEBO-CONTROLLED, CROSSOVER STUDY

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Background: Both IL-12 and IL-23 have been implicated in the pathogenesis of SLE. We have previously reported that treatment with an anti-IL-12/23 p40 monoclonal antibody ustekinumab (UST) resulted in greater improvement in several SLE disease measures through week 24 compared with placebo (PBO).¹

Objectives: Results of global and organ-specific disease measures and flares through 1 year are reported here.

Methods: We conducted a PBO-controlled phase 2 study in 102 patients with seropositive active SLE (defined by SLICC criteria, SLEDAI score ≥ 6 , and ≥ 1 BILAG A and/or ≥ 2 BILAG B scores). Patients were randomized (3:2) to UST (6 mg/kg single IV infusion, then 90 mg SC q8w beginning at week 8, n=60) or PBO (n=42), both added to standard background therapy. Patients receiving PBO crossed over to UST (90 mg SC q8w) at week 24. The primary endpoint was the proportion of patients achieving SLE Responder Index (SRI)-4 response at week 24. Modified intention-to-treat (mITT) analyses across SLE disease measures were performed to evaluate maintenance of response with UST between week 24 and week 48 and severe BILAG flares (≥ 1 new BILAG A score). Safety was assessed through week 56.

Results: As previously reported, SRI-4 response rate at week 24 was significantly greater (p=0.0057) in patients receiving UST (62%) vs PBO (33%).¹ In the UST group, SRI-4 (week 24: 62% vs week 48: 63%), SRI-5 (week 24: 43% vs week 48: 48%), and SRI-6 (week 24: 43% vs week 48: 47%) response rates were sustained at 1 year. Proportions of patients with ≥ 4 -point improvement from baseline in SLEDAI-2K score (week 24: 65% vs week 48: 67%) and with $\geq 30\%$ improvement from baseline in Physician's Global Assessment score (week 24: 68% vs week 48: 75%) were also maintained in the UST group. UST response

rates were also sustained through 1 year in organ-specific disease measures ($\geq 50\%$ improvement in active joint counts: week 24: 87% vs week 48: 87%; $\geq 50\%$ improvement in CLASI activity score: week 24: 53% vs week 48: 69%). In PBO patients who crossed over to UST at week 24 (n=33), response rates across outcomes studied were 10-20% higher at week 48 vs week 24. Flare rates for patients with severe BILAG flares were 2.1/10,000 patient-days in week 0-24 and 1.1/10,000 patient-days in week 24-48 in the UST group. In the PBO group, severe BILAG flare rates were 8.4/10,000 patient-days in week 0-24 and, following UST crossover, were 4.6/10,000 patient-days in week 24-48. The occurrence of severe BILAG flares seemed to diminish after approximately 8 weeks (week 8 in UST arm, week 32 in PBO arm) of treatment with UST (Figure). No deaths, malignancies, opportunistic infections, tuberculosis cases, or unexpected serious AEs (SAEs) were observed. Incidences of ≥ 1 SAE were UST (week 0-24) 8.3%, PBO (week 0-24) 9.5%, UST (week 24-48) 8.9%, and PBO-UST (week 24-48) 12.1%. Safety events were consistent with the known UST safety profile.

Conclusion: UST provided sustained clinical benefit in global and organ-specific SLE-activity measures and reduced flares through 1 year, with a safety profile consistent with other indications. Thus, UST may have durable therapeutic benefit in SLE.

Figure. Fewer patients treated with UST experienced severe BILAG flares

BILAG flare was defined as at least one new BILAG A domain score and/or at least 2 new BILAG B domain scores. All BILAG flares observed in this study were severe (BILAG A). Kaplan-Meier survival curves of the proportion of patients without severe BILAG flare are presented for the UST (closed circles, solid line) and PBO (open circles, dashed line) groups through week 48. The PBO group crossed over to UST at week 24. Counts include number of patients available at each study visit. Values for patients meeting treatment failure criteria are set to missing from the point of treatment failure forward.

UST, ustekinumab; PBO, placebo

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OP0042

LONG-TERM EFFECTS OF SYNERGETIC B CELL IMMUNOMODULATION WITH RITUXIMAB AND BELIMUMAB COMBINATION TREATMENT IN SEVERE, REFRACTORY SLE: TWO YEAR RESULTS

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Background: We conducted a phase 2, proof-of-concept study (SynBioSe study) in which we combined rituximab and belimumab (RTX+BLM) for treatment of SLE patients with severe, refractory disease. We have previously reported that RTX+BLM effectively reduced relevant anti-nuclear autoantibodies (ANAs) and showed a clinical response at 24 weeks¹.

Objectives: The aim of the present study is to investigate the long-term immunological and clinical effects of RTX+BLM in severe, refractory SLE patients.

Methods: Fifteen severe, refractory SLE patients were included and followed for 2 years. Patients received RTX at week 0 and 2 and BLM at week 4, 6, 8 and then 4-weekly until week 104. Clinical response was assessed by achievement of low level of disease activity (LLDAS). By using specific antibody assays and high sensitivity flowcytometry (HS-FACS), we longitudinally followed, respectively, levels of SLE-specific ANAs and B-cell subsets.

Results: Ten patients (67%) showed a good clinical response after 24 weeks, referred to as 'responders'. Two of these patients (13%) switched treatment after 24 weeks due to a pregnancy wish and 8 patients (53%) continued study treatment throughout the complete 2 years of follow-up. Five patients (33%) discontinued treatment due to persistent LN (n=2), major flare (n=2) or relapsing minor flare (n=1), together referred to as 'non-responders'. Responders achieved LLDAS at a median of 24 weeks [range 12-36] and remained in LLDAS for 76 weeks [56-92] out of 104 weeks of follow-up. In 7 patients with active LN, 6 attained a complete renal response. In responders, ANAs showed significant and specific reduction throughout 2 years with achievement of seronegative anti-dsDNA immunofluorescence in 6 out of 6 anti-dsDNA positive patients at baseline while total IgG, anti-tetanus and anti-rubella antibodies remained stable. By using HS-FACS, a median decrease of 97% [-99;+35] CD19+ B-cell depletion was achieved at 24 weeks. Long-term follow-up showed that B-cell repopulation was inhibited throughout 2 years with a persistent median decrease of 84% [-92;+22] compared to baseline. Further analysis of B-cell subsets revealed that in the responders, double negative (DN) B cells (CD27-IgD-) reached maximum depletion at 4 weeks (median 1.09×10^6 cells/liter [range 0.23×10^6 - 4.31×10^6]), which lasted up to week 72 with a median of 1.26×10^6 cells/liter [0.79×10^6 - 4.11×10^6] at week 72, similar to values at nadir. This was in contrast to non-responders, where maximum depletion of DN B-cells was reached at 12 weeks (0.48×10^6 [0.17×10^6 - 5.86×10^6]), after which these cells increased to 2.29×10^6 [0.49×10^6 - 4.39×10^6] at 24 weeks.

Conclusion: Over 2 years follow-up, RTX+BLM for severe, refractory SLE patients prevented complete B-cell repopulation with persistent and specific reduction of ANAs. Clinical response was observed in 67% of patients and treatment discontinuation due to high disease activity was associated with early repopulation of DN B-cells. These data warrant further studies on clinical and immunological benefits of combination treatment RTX+BLM.

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Trial registration: ClinicalTrials.gov NCT02284984

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OP0043

WITHDRAWAL OF A LOW DOSE (5 MG) OF CORTICOSTEROIDS IN SYSTEMIC LUPUS IN REMISSION FOR MORE THAN A YEAR IS AT RISK OF RELAPSE – THE CORTICOLUP TRIAL

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Background: Glucocorticoids (GCs) are a mainstay of treatment for patients with SLE but are associated with significant adverse effects. Some SLE patients are maintained for a long-term under a low dose of prednisone to prevent relapse. There is no scientific data to sustain this therapeutic strategy.

Objectives: We hypothesized that maintaining a daily dose of 5 mg prednisone in patients with an inactive SLE for at least a year would prevent the risk of relapse.

Methods: The CORTICOLUP study (NCT0255817) was a prospective randomized, open-labeled, controlled, monocentric study sought to compare

maintenance vs withdrawing of low-dose of prednisone (5mg) to reduce SLE flares, conducted from January 2014 to March 2017. Inclusion criteria were SLE patients **who during the year** preceding the inclusion had 1/an inactive SLE defined by a SLEDAI-2K score ≤ 4 , a BILAG-2004 index C, D or E in all systems and a PGA =0 and 2/a stable SLE treatment including prednisone 5 mg daily. The primary end point was the number of patients with flares during 12 months of follow-up defined by the revised-SELENA SLEDAI Flare Index (rSFI). Secondary outcomes were occurrence of a BILAG scores A or B ≥ 1 , clinical SLEDAI-2k >0 , PGA ≥ 0.5 and increase of the SLICC damage index (SDI). All patients were included in the intention-to-treat analysis.

Results: A total of 124 patients (61 in the maintenance group and 63 in the withdrawal group) were included. No patients were lost to follow up. At baseline there were no significant differences between the maintenance and the withdrawal group with respect to: duration of SLE [mean ($\pm$ standard deviation) duration of 11.8 (± 0.9) versus 13.1 (± 1.0) years], duration of remission [55.7 (± 5.8) vs 67.5 (± 6.8) months], HCQ treatment [98.2% vs 100.0%], immunosuppressive drugs [27.9% vs 25.4%], previous renal involvement [34.4% vs 41.3%], low C3 [16.4% vs 15.9%], positive Farr test [47.5% vs 46.0%], and SDI [mean index of 0.5 (± 0.1) vs 0.7 (± 0.2)].

There were significantly more flares in the withdrawal group compared to the maintenance group (17 flares versus 4, $p=0.0034$ using the Fisher's exact test). Mild or moderate flares were more frequent in the withdrawal group compared to the maintenance group (12 vs 3, $p=0.029$). The occurrence of severe flare was not significantly different between the two groups (5 vs 1, $p=0.208$). More than two-thirds of the flares in the withdrawal group occurred within the first six months. Within the withdrawal group, using forest plot analysis, no significant association was found between the occurrence of a flare and age, sex, duration of SLE, duration of SLE remission, duration of GCs treatment, immunosuppressants and serological SLE activity at randomization. Four patients in the withdrawal group and none in the maintenance group experienced damage: 2 osteoporosis bone fractures, 1 hydroxychloroquine retinopathy and 1 cataract.

Conclusion: Withdrawal of low dose of steroids in patients with inactive SLE and stable therapeutic regimen for more than a year is associated with a high risk of relapse.

Disclosure of Interests: None declared

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OP0044

A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE GONADOTOXIC EFFECTS OF CYCLOPHOSPHAMIDE AND BENEFITS OF GONADOTROPIN RELEASING HORMONE ANALOGUES IN WOMEN OF CHILD-BEARING AGE WITH AUTOIMMUNE RHEUMATIC DISEASE

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Background: Premature ovarian insufficiency (POI) is a side effect of intravenous cyclophosphamide (i.v.CYC), which is the treatment of choice for many severe manifestations of autoimmune rheumatic disease (ARD) (1). The risk of POI post-CYC appears to be dependent on cumulative dose and patient age but has not been precisely quantified. Gonadotropin Releasing Hormone Analogues (GnRHa) may reduce this risk (2). Studies however, on GnRHa and CYC use in ARD patients have been limited in size and/or by combined analysis with patients receiving CYC for malignancies.

Objectives: In order to more precisely categorise the risk of POI in ARD patients, and determine whether GnRHa are effective in reducing this risk, we performed a systematic review to assess the risk of sustained amenorrhoea with i.v.CYC in ARD and a meta-analysis of the efficacy of GnRHa in reducing this risk.

Methods: Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses principles, we searched English language papers using Pubmed, MEDLINE, EMBASE and the Cochrane Library to April 2018. We included all studies