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.