46% and 25% of ABA- and PBO-treated pts, respectively, but this was not enriched for any specific event and there were no new ABA safety signals.

Conclusion: Despite favourably impacting biomarkers of disease activity, abatacept therapy was no better than PBO for improving the clinical measures of disease. These results do not indicate a clinical benefit of abatacept in pSS.

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Methods: Splenocytes of syngeneic NZB/F1 (NZB) donor mice were incubated with mitomycin C and injected into recipient’s tail vein after matching for age and disease activity. Group 1 received no MCT therapy, group 2 standard-dose MCT therapy with 1.5x10^8/kg BW once and group 3 repeated MCT therapy with 1.5x10^8/kg BW at weeks 1, 2 and 3. Group 4 received MIC infusions before disease onset as preemptive treatment approach. Disease activity was monitored by loss of body weight, protein excretion, serum creatinine and dsDNA antibodies. Combined primary endpoint was day 40 post-treatment, protein excretion >3g/l for 2 consecutive weeks and >30% loss of original body weight. Histopathology with PAS and HE staining was performed to assess degree of lupus nephritis. Regulatory cell subsets were measured in peripheral blood.

Results: MIC therapy prevented the progression of fatal lupus nephritis in NZB mice. Protein excretion, serum creatinine and dsDNA antibodies were lower in standard-dose (group 2) and preemptive (group 4) groups compared to control group (group 1) whereas repeated MCT therapy after disease onset had no effect (Figure 1A-E). The primary endpoint was reached significantly more often in control group (1, 67%) compared to treatment groups 2 (14%), 3 (14%) and 4 (0%) (Figure 1F). Renal architecture was preserved in different MIC treatment groups.
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+CD19dim 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 approach in SLE models (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 autoreactive 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-CROSSOVER, CONTROLLED 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 6, 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 (32%). In the UST group, SRI-4 (week 24: 62% vs week 48: 63%), SRI-6 (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 ≥30% improvement from baseline in Physician’s Global Assessment score (week 24: 66% 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 (≥50% improvement in active joint counts: week 24: 87% vs week 48: 87%; ≥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, 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.

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OP0042
LONG-TERM EFFECTS OF SYNERGETIC B CELL IMMUNOMODULATION WITH RITUXIMAB AND BELUMINAB COMBINATION TREATMENT IN SEVERE, REFRACTORY SLE: TWO YEAR RESULTS
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Background: We conducted a 2 phase, 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 weeks.

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.