Supplemental Methods:

MSC derivation:

Umbilical cords were digested into single cells and cells were cultured in Minimum Essential Medium (MEM) Alpha Modification (1X) with 5% human serum albumin until passage 2. Cells were then pelleted and resuspended in culture media and then added to an equal volume of cold 2X concentrated freezing media composed of 10% human serum albumin (Grifols), 20% DMSO (Cryoserv Bionichepharma) and Gibco Minimum Essential Medium (MEM) Alpha Modification (1X). MSCs were frozen at a rate of 1°C per minute. After reaching -100°C, the sample vials were transferred to a liquid nitrogen storage container and the cells were housed in vapor phase at -140°C.

To thaw cells, the vials were retrieved and submerged in a 37°C water bath. Thawed cells were spun down to remove DMSO and then resuspended in culture media for expansion. MSC cell density and morphology were inspected daily. For quality measures, samples were taken and tested for bacterial (aerobic & anaerobic), fungal, endotoxin, and mycoplasma presence. A stat-Gram stain was performed and examined for any microscopic or vegetative organisms. Cells were suspended in a 0.5% human serum albumin (Baxter) and PlasmaLyte-A (Baxter Deerfield, IL USA) Solution at $2x10^6$ cells/ml, put into an i.v. bag, kept at room temperature and prepared for injection.

Immunophenotyping of MSCs was performed using flow cytometry to verify purity of >95% prior to administration. The following markers were analyzed: CD44, HLA II (DR), HLA I, CD73, CD90, CD31, CD45, and CD105 (BD-Bioscience, USA). Potency of MSCs was assessed via peripheral blood mononuclear cell (PBMC) proliferation assay to determine T cell proliferation and interferon-gamma (IFNγ)-stimulated expression of IDO. Only MSC lots that fulfilled criteria for purity, immune potency and sterility were released for study participant infusion.

Patient Inclusion and Exclusion criteria: Patients were excluded that had active CNS lupus affecting mental status or active lupus nephritis requiring dialysis. Laboratory exclusions were an eGFR <30, WBC <2.0/mm^3, hemoglobin <8 g/dL, platelet count <30,000/mm^3, liver enzymes AST or ALT >4 times upper limit normal. Patients with positive testing for HIV, hepatitis B (other than HepBsAb) or hepatitis C were excluded as were individuals with a history of malignant neoplasm within the last 3 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix. Pregnant or breastfeeding mothers were excluded as were females of childbearing potential not willing to use adequate contraception. Other exclusions were a history of renal transplantation, herpes zoster within the past 90 days or any infection requiring hospitalization or intravenous antibiotics within the past 60 days. Clinically significant EKG or chest x-ray changes as judged by the investigators were exclusionary. Any other medical condition related or unrelated to SLE, which, in the opinion of the investigator, would render the patient inappropriate or too unstable to complete study protocol were not enrolled. Use of prednisone >0.5 mg/kg/day (or equivalent corticosteroid) within 1 month of Baseline visit or change or additions to their immunosuppressant regimen within 3 months of Baseline visit (except corticosteroids) led to exclusion as did use of other experimental therapeutic agents within 3 months of Baseline visit. Receiving belimumab within 3 months of Baseline or having received rituximab within 6 months of Baseline led to exclusion. Comorbidities requiring oral, IV, IM or IA corticosteroid therapy were exclusionary. Current substance abuse or recent (within 60 days) history of substance abuse made individuals ineligible for the trial.

Safety Measures:

To further assess safety, a complete metabolic profile (CMP, or chemistry panel), CBC with WBC differential and platelets, C3, C4, Anti-ds DNA, Urinalysis, Urine Protein/Creatinine Ratio, pregnancy tests, as well as physical exams were performed at each of the 12 study visits (Screening, baseline, wks 1, 2, 4, 8, 12, 16, 20, 24, 36 and 52). Additional blood was obtained at baseline, week 4, 8 and 24

for mechanistic studies. Medical history was collected at screening and baseline and adverse events occurring after start of study therapy were recorded.

Study participants were asked to answer patient completed questionnaires including the PROMIS Depression SF. If a participant answered any questions on this scale indicating depression, they would be referred to a specialist for treatment, although this did not occur in this study. SF-36 and Lupus Qual were also collected at each visit.

Safety endpoints followed in this trial: Adverse events and SAEs were assessed at each visit to assess tolerability and safety. All Grade 2-5 adverse events, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) system, were defined as possibly, probably, or definitely related to SLE. All Grade 2-5 adverse events, as defined by the CTCAE system, which were defined as possibly, probably, or definitely related to the study infusion.

A DSMB meeting, consisting of 4 expert individuals at other institutions uninvolved in the trial, included three lupus clinicians and a statistician, was held by teleconference between 2 and 4 weeks after each patient was dosed. Adverse events, lab data and patient disease activity scores were discussed. The DSMB then made recommendations regarding whether the study could continue. After the first patient, the AEs and progress of all the patients was reviewed at each DSMB meeting. At each meeting the DSMB voted to allow the study to continue.

Treatment Details

Patients were permitted to initiate or increase prednisone (or equivalent corticosteroid) up to 0.5 mg/kg/day at the time of enrollment into the study. The decision regarding prednisone dose and tapering instructions were at the discretion of the treating physician. This allowed some relief of symptoms of active lupus while awaiting screening results and, while awaiting the preparation and infusion of the cells. Participants took prednisone (or equivalent corticosteroid) up to 0.5 mg/kg/day during the study with the goal of tapering to 10 mg/day or lower by Week 20 and maintained 10 mg/day or lower by Week 24.

Patients were permitted to continue on their SOC immunomodulatory regimen, as long as the medication and dose were stable for 3 months prior to the baseline visit. Patients with active lupus nephritis had to have completed at least 6 months of immunosuppressive therapy prior to the baseline visit. No dose increases or new additions to SOC immunosuppressant therapy could be made during the study until after the Week 24 primary endpoint assessment, unless those changes were considered medically necessary by the treating physician for the participant's SLE activity, in which case, the participant was considered a treatment failure.

All subjects had access to any care deemed medically necessary, but administration of rituximab/belimumab or other B cell depleting biologic therapy, addition of any new immunosuppressant agent not part of the SOC regimen at the time of screening or any experimental therapy was considered a treatment failure and major protocol deviation.

Mechanistic Study Methods

Isolation of PBMCs

Patient blood was collected into BD vacutainer CPT tubes with sodium heparin at baseline and then subsequent weeks 4, 8, and 24 post-treatment. Briefly, tubes were centrifuged and the layer containing PBMCs was collected from each tube. PBMCs were washed once with cold isolation buffer and counted with a Countess automated cell counter (Invitrogen). A portion of PBMCs was set aside for flow cytometric analysis and the rest were cryopreserved.

B cell phenotyping by Flow cytometry.

Blood samples were collected from patients in CPT tubes (BD) at baseline, week 4, 8 and 24, then shipped overnight to Emory University. Mononuclear cells from the peripheral blood (PBMCs) were isolated the day of arrival by Ficoll-Paque density gradient centrifugation. For flow cytometry analysis of the B cell subsets, PBMCs were stained at 4°C for 30 minutes in FACS buffer (PBS with 0.5% BSA) with a cocktail of fluorochrome-conjugated antibodies against the following markers: CD19-APC-Cy7 (SJ25C1, BD), CD3-PerCP-Cy5.5 (SP34-2, BD), IgD-FITC (IA6-2, BD), CD27-BV605 (L128, BD), CD38-PE-Cy7 (HIT2, eBioscience), CD24-PE-AF610 (SN3, ThermoFisher), CD21-PE-Cy5 (B-ly4, BD), CD11c-PE (B-ly6, BD), CD138-APC (44F9, Miltenyi) and 9G4-Pacific Blue. After washing off unbound antibodies, cells were stained with Fixable Viability Dye eFluor506 (eBioscience) in PBS at 4°C for 15 minutes to provide a live and dead discrimination. Cells were then fixed with 0.5% formaldehyde in PBS and washed with FACS buffer before they were acquired on a LSRII Flow Cytometer (BD). Flow cytometry data were analyzed with Flowjo software.

T cell Flow Cytometry

Panels were designed to identify various T cell subsets, including Th1 (from Biolegend: CD4 APC-Cy7 RPA-T4, CXCR3 Brilliant Violet 421 G025H7, CCR5 Alexa Fluor 488 J418F1, CD28 PE-Cy7 CD28.2, Tbet Alexa Fluor 647 4B10), Th2 (from Biolegend: CD4 APC-Cy7 RPA-T4, CRTH2 APC BM16; from BD Biosciences: CCR4 V450 1G1, GATA-3 PE-Cy7 L50-823), Th17 (from Biolegend: CD4 APC-Cy7 RPA-T4, CCR6 FITC G034E3, CD161 PerCP-Cy5.5 HP-3G10; from eBioscience: ICOS PE-Cy7 ISA-3, RORγT APC AFKJS-9), T follicular helper (Tfh; from Biolegend: CD4 APC-Cy7 RPA-T4, CXCR5 PerCP-Cy5.5 TG2, Bcl-6 APC 7D1; from BD Bioscience: PD-1 FITC MIH4; from eBioscience: ICOS PE-Cy7 ISA-3) or Tregs (from Biolegend: CD4 APC-Cy7 RPA-T4, CD25 FITC BC96, GARP PE 7B11, Neuropilin-1 PerCP-Cy5.5 12C2, FoxP3 Alexa Fluor 647 150D, Helios Brilliant Violet 421 22F6; from eBioscience: Latency Associated Peptide PE-Cy7 FNLAP). Fresh PBMCs were washed twice in FACS buffer (PBS containing 2% heat-inactivated fetal bovine serum), resuspended in FACS buffer containing extracellular antibodies at a 1:200 dilution and incubated for 30 minutes at 4°C. After two subsequent washes with FACS buffer, cells were fixed and stained for intracellular transcription factors using a FoxP3/Transcription Factor Staining Buffer Set (eBioscience) according to manufacturer's instructions. Samples were immediately acquired on a FACSVerse flow cytometer (BD) and analyzed using FlowJo software.

GARP and TGFβ ELISA

Detection of GARP-TGFβ complexes, GARP-LAT complexes and soluble GARP levels were performed by ELISA (39).

De-identified whole blood samples were received from the MUSC Lupus Biorepository in heparin-coated tubes. Peripheral blood lymphocytes were isolated using a Ficoll-Paque PLUS gradient (GE Healthcare). Serum was collected in serum separation tubes (SST) tubes and processed according to manufacturers' protocol (BD). Patient samples were collected according to an approved protocol by the Medical University of South Carolina Institutional Review Board. Written informed consents from all included subjects were obtained prior to participation, and the project fulfilled the Helsinki Declaration.

Flow cytometry for GARP

After Fc-receptor blocking, PBMC were stained for surface markers in FACS buffer. Antibodies against human CD19 (Clone: HIB19), CD38 (HIT2), CD138 (DL-101), CD4 (OKT4), FoxP3 (RPA-T4), GARP (G14D9), LAP (TW4-2F8) were purchased from ebioscience/ThermoFisher. Samples were analyzed on a BD LSR cytometer and analyzed by FlowJo software (Tree Star). Viability of the cells analyzed was ensured by gating on singlets and live cells, as indicated by the lack of 7-AAD or Fixable Viability Dye (Affymetrix).

ELISA for GARP

To measure active and total TGF-β1 in serum, ELISA plates (Corning) were coated overnight at 4°C with anti-mouse/human TGF-β1 capture antibody (BioLegend), followed by blocking with 1% BSA for 1 hour at room temperature. Samples were treated with HCl for 10 mins and neutralized with Tris/NaOH to obtain total TGF-β. Both active and total TGF-β1 were detected using Biotin-anti-TGF-β antibody (BioLegend), Strepdavadin-HRP (BioLegend), and TMB Substrate reagents (BD). To detect soluble GARP in human serum, a GARP ELISA kit was used according to the manufacturer's protocol (BioLegend). Immunoglobulin A levels were detected in serum using a Human IgA ELISA Kit according to manufacturer's protocol (Invitrogen).

ENA autoantibody serum assays

A luciferase immunoprecipitation assay was used to measure anti-52kRo, anti-60kRo, anti-Sm and anti-RNP. The serum from weeks 0, 4, 8 and 24 were measured by the Luciferase Immunoprecipitation system (LIPs) assay using the manufacturer's protocol. Normal control sera were used to set the upper limits of normal.

Subject	***Baseline***	***Week 4***	***Week 8***	***Week 12***	***Week 24***	***Week 52***	***Change in SLEDAI 0-24/52***
1	**6**	4	2	0	**0**	0	***-6/-6***
2	**8**	8	8	2	**2**	2	***-6/-6***
3	**6**	12	8	-	**-**	-	
4	**10**	8	15	10	**6**	2	***-4/-8***
5	**8**	2	0	2	0	0	***-8/-8***
6	**11**	5	8	8	**5**	3	***-6/-8***

Supplemental Table 1: SLEDAI scores at each timepoint. S Table 1 presents the SLEDAI scores of the patients from baseline to week 52. Participant 3 dropped out at week 8 so the data for the following weeks was unattainable. Week 24 was the time when the primary endpoint was determined. The change in SLEDAI score is presented in the final column from baseline to week 24/52.

Patient number-week	**SLEDAI**	**Resting Naïve transitional P=0.042**	**Double negative P=0.041**	**Double negative 2**	**Switched memory P=0.007**
Patient 1 week 0	6	43	42	19	10
Patient 1 week 24	0	83	10	3	2
Patient 1 Week 0-24 Change	**-6**	**+40**	**-32**	**-16**	**-8**
Patient 2 week 0	8	32	32	3	1
Patient 2 week 24	2	78	8	1	1
Patient 2 Week 0-24 Change	**-6**	**+46**	**-24**	**-2**	**0**
Patient 4 week 0	10	82	7	3	4
Patient 4 week 24	6	80	18	3	4
Patient 4 Week 0-24 Change	**-4**	**-2**	**+11**	**0**	**0**
Patient 5 week 0	8	58	18	1	12
Patient 5 week 24	0	82	5	1	4
Patient 5 Week 0-24 Change	**-8**	**+24**	**-13**	**0**	**-8**
Patient 6 week 0	11	46	42	9	6
Patient 6 week 24	5	83	11	3	2
Patient 6 Week 0-24 Change	**-6**	**+37**	**-31**	**-6**	**-4**

Supplemental Table 2: Numerical summary of the B cell subset changes presented graphically in Figure 2. As noted there are significant decreases in double negative B cells and switched memory B cells with a compensatory increase in resting naïve and transitional B cells from baseline to week 24. Data presented are the percent of CD19 B cells. There were no significant changes in overall B cell numbers. Data from Patient 3 is not included due to having no week 24 sample. Figures represent the percentage of CD19 B cells in each sample. Numbers do not add up to 100% as DN2s are also counted as DNs and not all B cell subsets are presented in the Table

Supplemental Figure Legends

Supplemental Figure 1A- Extranuclear nuclear antigen autoantibody assay over time. Anti-Ro52, Ro60, Sm and RNP autoantibodies were determined by the LIPS assay. Reference value for each assay was derived from a group of healthy controls (n=30), and mean+2sd was chosen as the cutoff as indicated by the double dotted line. Week 8 data is missing from some patients due to weather induced missed deliveries of samples. **Supplemental Figure 1B-** T cell subset changes over time presented as percent of CD3+ peripheral blood PBMCs. Results using total numbers of T cell subsets revealed similar results to the percentages. There were some individual changes, but overall there was not a significant change in any T cell subset. Results for TfH and TpH subsets are also presented with small overall percent and number and no change overall within the group other than variable changes in individuals that were not consistent.