Abstract CT-04 Table 1

Subject	Baseline Age, Race/Ethnicity, Sex	SLEDAI Score					Non-Serious AEs (#)	SAE (#)
		Baseline	Week 4	Week 8	Week 12	Week 24		
1	32 yo Black Female	6	4	2	0	0	3 Grade 1 5 Grade 2 0 Grade ≥ 3	0
2	38 yo Caucasian Female	8	8	8	2	2	0 Grade 1 2 Grade 2 0 Grade ≥ 3	0
3	33 yo Caucasian Female	6	12	8	Dropped out	Dropped out	2 Grade 1 2 Grade 2 0 Grade ≥ 3	1
4	26 yo Hispanic Female	10	8	15	10	6	0 Grade 1 3 Grade 2 0 Grade ≥ 3	0
5	48 yo Caucasian Female	8	2	0	2	0	1 Grade 1 1 Grade 2 0 Grade ≥ 3	0
6	38 yo Black Female	11	5	8	8	5	1 Grade 1 1 Grade 2 0 Grade ≥ 3	0

Methods Patients (n=6) with active SLE (SLEDAI ≥ 6) who signed informed consent and met all inclusion and exclusion criteria sequentially received 1×10^6 cells/kg umbilical cord-derived MSCs given as an IV infusion in Plasma-Lyte A solution. Post-infusion, Week 1 and 2 safety data from each participant was reviewed by the Data Safety Monitoring Board prior to enrolling the next patient. Primary safety and efficacy endpoints were determined at Week 24. Each patient is followed for a total of 52 weeks.

Results Table 1 summarizes the demographics, visit SLEDAI scores, number of serious and non-serious adverse events (SAEs, AEs). The 6th participant completed their Week 24 visit on April 11, 2018. To date, there has been 1 SAE, deemed not unexpected and not attributed to investigational product. No non-serious AEs higher than Grade 2 by NCI-CTCAE scoring were reported. The SAE was prolonged hospitalization following a partial dose infusion of rituximab IV leading to anaphylaxis. Rituximab was started for persistent SLE disease activity (patient dropped out of the study after Week 8) and was given in the hospital ICU setting due to her prior history of anaphylaxis to Tween (polyethoxylated surfactant found in IV and SQ medications). Anaphylaxis resulted in a prolonged hospital stay of 2 days, resolving with treatment without sequelae. The SAE was attributed to her known allergy to ingredients in the rituximab infusion and deemed unrelated to the MSCs that she received several months earlier. The AEs 'possibly' attributable to the investigational product were Grade 2 nausea, Grade 2 tachycardia, and Grade 1 flushing with Grade 1 toe paresthesias – all of which resolved without sequelae.

Among the 5 patients who completed their Week 24 evaluations, all showed improved SLE activity (mean SLEDAI score 8.6 ± 1.9 at Baseline improved to 2.6 ± 2.8 at Week 24) with stable or lower doses of prednisone and stable background immunosuppressants. Mean physician global assessment (PGA) scores also improved from 1.71 ± 0.48 at Baseline to 0.32 ± 0.17 at Week 24.

Conclusions A single-dose of umbilical cord-derived MSCs was safe and well-tolerated in this open-label phase I trial for 6 patients with active SLE. Initial efficacy data for MSCs in SLE appears promising and will be further tested in a larger controlled trial.

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Trial registration NCT 03171194

CT-05 ALTERNATIVE AVAILABLE DRUG DEVELOPMENT PATHWAYS IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Background Development of drugs in SLE is difficult for many reasons including the heterogeneity of the disease, the outcome measures used to define responsiveness which are cumbersome, poorly responsive to change and have little relationship to clinical practice. The drugs targets are potentially immunosuppressive in an immunologically compromised host. Regulatory agencies require large safety databases associated with the development programs. Consideration of alternate pathways for approval may be warranted. In Europe and the US the Orphan Drug Designation allows for therapies to be approved on far smaller data bases, at typically less cost and patient burden.

Methods In the US, the US FDA requires the disease or condition for which the drug is intended will affect fewer than 2 00 000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 2 00 000 per year. Alternatively, for a drug intended for diseases or conditions affecting 2 00 000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 2 00 000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States. In the US, if a sponsor requests orphan-drug designation for a drug for only a subset of persons with a particular disease or condition that otherwise affects 2 00 000 or more people ('orphan subset'), a demonstration that, due to one or more properties of the drug, the remaining persons with such disease or condition would not be appropriate candidates for use of the drug.

In Europe, the EMA expects that the disease is either life-threatening or debilitating, the medical plausibility of the proposed orphan indication; and importantly, that the prevalence of the condition in the European Union is not more than five in 10,000; or that it is unlikely that marketing the medicinal product in the European Union, without incentives, would generate sufficient return to justify the necessary investment; and furthermore, that no satisfactory method of diagnosis prevention or treatment exists, or if such a method exists, that the medicinal product will be of significant benefit to those affected by the condition.

An example of a prevalence analysis in SLE is shown in table 1.

Abstract CT-05 Table 1 Prevalence of non-class III-VI LN SLE

Parameter	Estimate	Source
U.S. Population Estimate	320,000,000	U.S. Census Bureau (2014), July 2014 estimate
Overall U.S. Prevalence of SLE	97 per 1 00 000 (n=310,400)	Upper confidence limit of most conservative SLE prevalence estimate from Lim et al. (2014)
Proportion of SLE patients with LN	50% (n=155,200)	Dooley 2007 and Mok et al. 2013
Proportion of LN patients with Class III-Class VI LN	92% (n=142,784)	Mok et al., 2013
Orphan population of SLE among patients with no Class III-Class VI LN	n=1 67 616	–

CT-06 MISSING OUTCOMES IN SLE CLINICAL TRIALS: IMPACT ON ESTIMATING TREATMENT EFFECTS

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Background Missing data due to drop-out and loss to follow-up is a common problem in SLE trials. The usual approaches for handling this issue include analyzing only subjects with complete data (complete case analysis; CC), last observation

carried forward (LOCF), or imputing non-responses for missing outcomes (non-responder imputation; NRI). However, the validity of these methods depends on strong assumptions about the missing data mechanism. Multiple imputation (MI) is a flexible model-based technique that accounts for uncertainty in the imputation process by generating several possible values for the missing data, resulting in multiple complete data sets. These are analyzed separately and results are combined. MI is being used more widely in different disease settings but has not been applied to analyze the primary outcome in a SLE trial. We explored the use of MI to address missing data in the composite outcome, SLE Responder Index (SRI)–5, using data from patients assigned to standard of care (SoC) in a 52 week trial.

Methods Data on 279 SLE patients randomized to SoC for 52 weeks who were receiving mycophenolate mofetil (MMF), azathioprine, or methotrexate at entry were obtained from the Lupus Foundation of America-Collective Data Analysis Initiative database. Multiple imputation using chained equations was applied to handle missing data in an analysis to evaluate differences in SRI-5 response rates at 52 weeks between patients on MMF and the other immunosuppressants (non-MMF). Three different imputation models were considered that included various combinations of longitudinal measures of disease activity (both composite and individual measures) and patient characteristics. Results were compared to estimates using the CC, LOCF, and NRI.

Results Missing data rates were 32% in the MMF and 23% in the non-MMF groups. As expected, the NRI missing data approach yielded the lowest response rates; the smallest and least significant estimates of between group differences were observed with LOCF (table 1). Group differences were magnified with all three MI models compared to results of other methods. Imputing SRI-5 directly (MI-1) versus the individual components (MI-2) yielded nearly identical results.

Conclusions Given the limitations of conventional approaches for handling missing data, the MI method should also be considered in SLE trials. However, results can vary depending on the imputation model that is used, and the assumptions required for validity of this and other missing data methods must be justified. Sensitivity analysis using different approaches is important to demonstrate robustness of results especially when missing data rates are non-negligible.

Abstract CT-06 Table 1 SRI-5 response rates at 52 weeks on SoC by immunosuppressant use

Missing data approach	Non-MMF	MMF	Difference	95% CI	P-value
CC	46.8%	29.3%	17.5%	1.7% to 33.3%	0.043
LOCF	40.6%	30.0%	10.6%	–2.7% to 23.9%	0.13
NRI	36.1%	20.0%	16.1%	4.1% to 28.0%	0.019
MI-1*	47.6%	28.5%	19.1%	4.6% to 33.5%	0.010
MI-2*	46.0%	27.0%	19.0%	4.3% to 33.6%	0.011
MI-3*	47.6%	29.7%	17.9%	3.1% to 32.7%	0.018

*n=40 imputed data sets; MI-1: Imputation model includes MMF status, race, baseline values of SLEDAI, PGA, BILAG score, protein/creatinine ratio, anti-dsDNA, SRI-5 at 12, 24, 36, 44, 52 weeks; MI-2: Imputation model same as MI-1 but separately imputing components of SRI-5 (SLEDAI, BILAG, PGA); MI-3: Imputation model includes MMF, SRI-5 at all time points.

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