<<st2>>ORIGINAL ARTICLE

<<rrh>>MMF and Oral CYC Efficacy on Skin Thickness

<<lrh>>Namas et al

<<title>>Efficacy of Mycophenolate Mofetil and Oral Cyclophosphamide on Skin Thickness: Post Hoc Analyses From Two Randomized Placebo-Controlled Trials

<<aut>>RAJAIE NAMAS,[1] DONALD P. TASHKIN,[2] DANIEL E. FURST,[2] HOLLY WILHALME,[2] CHI-HONG TSENG,[2] MICHAEL D. ROTH,[2] SUZANNE KAFAJA,[2] ELIZABETH VOLKMANN,[2] PHILIP J. CLEMENTS,[2] AND DINESH KHANNA[1]

<<ftnts>>ClinicalTrials.gov identifiers: NCT00004563 and NCT00883129.

Supported by the NIH (U01-HL-60587, U01-HL-60606, R01-HL-089758, R01-HL-089758, and R01-HL-089901). Drs. Wilhalme, Tseng, and Khanna's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR-063120).

[1]Rajaie Namas, MD, Dinesh Khanna, MD, MS: University of Michigan Scleroderma Program, Ann Arbor; [2]Donald P. Tashkin, MD, MS, Daniel E. Furst, MD, Holly Wilhalme, MS, Chi-hong Tseng, PhD, Michael D. Roth, MD, Suzanne Kafaja, MD, Elizabeth Volkmann, MD, MS, Philip J. Clements, MD: David Geffen School of Medicine, University of California, Los Angeles. Participants in the Scleroderma Lung Study I and members of the Scleroderma Lung Study II Research Group are listed in Appendix A.

Address correspondence to Dinesh Khanna, MD, MS, Professor of Medicine, Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48103. E-mail: khannad@med.umich.edu.

Submitted for publication January 12, 2017; accepted in revised form May 16, 2017.</ftnts>>

<<abs>>

Objective. To assess the efficacy of mycophenolate mofetil (MMF) and cyclophosphamide (CYC) on modified Rodnan skin score (MRSS) in participants enrolled in the Scleroderma Lung Study (SLS) I and II.

Methods. SLS I participants received daily oral CYC or matching placebo for 1 year, whereas SLS II participants received daily MMF for 2 years or daily oral CYC for 1 year followed by placebo for second year. We assessed the impact of MMF and CYC on the MRSS in SLS II over a 24-month period. We also compared the change in MRSS in patients with diffuse cutaneous systemic sclerosis (dcSSc) assigned to CYC and MMF in SLS II and SLS I versus placebo in SLS I over a 24-month period using a linear mixed model.

Results. In SLS II, the baseline mean ± SD MRSS was 14.0 ± 10.6 units for CYC and 15.3 ± 10.4 units for MMF; 58.5% were classified as dcSSc. CYC and MMF were associated with statistically significant improvements in MRSS from baseline over the period of 24 months in dcSSc ($P < 0.05$ at each time point), but there were no differences between the 2 groups. In the dcSSc subgroup, the change in MRSS from baseline to all 6-month visits was similar in SLS II groups (MMF, CYC, pooled cohort [MMF + CYC]) and in the SLS I CYC group and showed statistically significant improvements compared to SLS I placebo at 12, 18, and 24 months ($P < 0.05$).

Conclusion. In SLS II, MMF and CYC treatment resulted in improvements in MRSS in patients with dcSSc over 24 months. In addition, MMF and CYC treatment resulted in statistically significant improvements in MRSS in patients with dcSSc when compared with the SLS I placebo group.

<<</abs>>

<<hd1>>**INTRODUCTION**

Systemic sclerosis (SSc) is an autoimmune disease characterized by skin thickening and internal organ involvement. Skin thickening is a hallmark of SSc, present in approximately 90% of patients. The severity and distribution of skin thickening can be quantified using the modified Rodnan skin score (MRSS). MRSS meets the Outcome Measures in Rheumatology filters of truth, feasibility, and discrimination, and has been shown to differentiate potentially disease-modifying drugs from placebo in randomized controlled trials (1–3).

<<significance&innovations>>

Significance & Innovations

- Treatment of scleroderma-related interstitial lung disease with mycophenolate mofetil for 2 years or cyclophosphamide for 1 year in the diffuse cutaneous subset of the participants in 2 randomized controlled trials resulted in statistically significant improvements in skin thickness.

Various immunosuppressive agents have been studied as potential disease-modifying therapies for skin thickening and interstitial lung disease (ILD) in SSc. Methotrexate (MTX) was evaluated in 2 randomized, double-blinded, placebo-controlled studies in early diffuse cutaneous SSc (dcSSc), and a trend toward statistically significant improvement in MRSS over a 12-month period with oral MTX and a significant improvement over a 24-week period with injectable MTX was observed (4,5). Two pivotal studies assessed cyclophosphamide (CYC) versus placebo in SSc-associated ILD: the Scleroderma Lung Study (SLS) I and the Fibrosing Alveolitis in Scleroderma Trial (FAST). Both studies demonstrated statistically significant efficacy or trends favoring efficacy in forced vital capacity percent predicted (FVC) with either oral CYC for 1 year (6) or intravenous monthly infusions of CYC for 6 months followed by daily azathioprine for 6 additional months (7). The SLS I trial also demonstrated a statistically significant difference in MRSS between the 2 groups (CYC versus placebo) in participants with dcSSc over a 12-month period, largely driven by the dcSSc group (6). In addition, the recently completed SLS II study demonstrated that oral daily CYC over a 1-year period, followed by a year of placebo, is equally effective in improving FVC percentage as daily mycophenolate mofetil (MMF) over a 2-year period (8). In addition, improvement in MRSS was similar in the 2 groups. Furthermore, CYC and MMF have been assessed in several uncontrolled studies showing a beneficial effect on MRSS (9–13).

Although the SLS I and II trials provided top-line results on the impact of CYC and MMF on MRSS, an in-depth analysis of the effect of CYC and MMF on MRSS has not been performed. Given the widespread use of immunosuppressives, especially MMF, in the management of SSc skin involvement without randomized controlled trials demonstrating its efficacy, we sought to address this gap by evaluating the 2 patient-level sets of data from the SLS I and II to assess whether CYC and MMF are superior to placebo for the management of skin thickness. Thus, our objectives for post hoc analyses were, first, to assess the separate and comparative impact of each study drug in SLS II (MMF and CYC) on MRSS over 24 months,

and, second, to compare the improvement in MRSS in the placebo and CYC arms of the SLS I versus the CYC + MMF and MMF arms of the SLS II at 6, 12, 18, and 24 months.

<<hd1>>**PATIENTS AND METHODS**

In SLS I, 158 participants with SSc-associated ILD were enrolled, and 142 in SLS II. SLS I and II received institutional review board approval at each medical center, and all participants signed an informed consent form. The inclusion criteria for enrollment were similar for both studies and were as follows: age >18 years, duration of disease within 7 years from onset of the first non-Raynaud's symptom of SSc, FVC 40–85%, diffusing capacity for carbon monoxide (DL_{CO}) ≥40% predicted (or 30–39% predicted in the absence of clinical evidence of pulmonary hypertension), and evidence of any ground glass opacities and/or positive bronchoalveolar lavage (≥3% neutrophils and/or ≥2% eosinophils).

In SLS I, participants received daily oral CYC (≤2 mg/kg body weight per day as tolerated) or matching placebo for 1 year, and were followed for an additional year (6). The study drug CYC was supplied by Bristol-Myers Squibb. MRSS was assessed at baseline and then every 3 months up to 24 months. The mean absolute difference in the primary outcome measure, the adjusted 12-month FVC, between the CYC and placebo groups was 2.53%, favoring CYC ($P < 0.03$), but the effect on FVC dissipated at 24 months (14). There were also treatment-related differences in physiologic and symptom outcomes at 12 months. There was a greater frequency of adverse events in the CYC group, but the difference between the 2 groups in the number of serious adverse events was not significant.

In SLS II, participants received daily MMF (≤3 gm daily as tolerated) for 2 years or daily oral CYC (≤2 mg/kg body weight as tolerated) for 1 year, followed by placebo twice daily for an additional year (8). The study drug MMF and matching placebo were supplied by Hoffmann-La Roche/Genentech. MRSS was assessed at baseline and then every 3 months up to 24 months. The adjusted FVC improved from baseline to 24 months by 2.19% in the MMF group and by 2.88% in the CYC group; the course of the FVC did not differ significantly between the 2 treatment groups based on the prespecified primary analysis ($P = 0.24$). MMF was better tolerated than CYC, with fewer patients who took MMF (compared to CYC) prematurely withdrawing from the study drug.

<<hd3>>**Statistical analysis.** Demographic and clinical characteristics were compared using Student's *t*-test for continuous variables and the chi-square test for categorical variables. Change in MRSS was calculated as the difference between MRSS at baseline and at 6, 12, 18, and 24 months; a linear mixed-effects model with a random subject effect and fixed effects for group (SLS I CYC, SLS I placebo, SLS II CYC, and SLS II MMF + CYC), month, the interaction between group and month, and baseline MRSS was used to predict the change in MRSS. Stratified analyses were conducted by study (SLS I versus SLS II), SSc subtype, and treatment group. The minimum clinically important difference (MCID), i.e., the smallest difference in a measure or instrument of interest that is considered to be worthwhile or important to the patient, was evaluated in the dcSSc subset and defined as a change in the MRSS of ≥5.0 units (15). Missing data were handled by the linear mixed model, and results with a *P* value of less than or equal to 0.05 were considered statistically significant. All statistical analyses were performed using SAS, version 9.4.

<<hd1>>**RESULTS**

<<hd3>>**Patient characteristics.** A total of 158 participants were enrolled in SLS I, and of those, 145 participants (91.8 percent), including 73 in the CYC subgroup and 72 in the placebo subgroup, were evaluated for the primary outcome. In SLS II, at baseline, the total cohort included 142 participants (limited cutaneous [lcSSc] 33 CYC and 26 MMF, dcSSc 40 CYC and 43 MMF). The total cohort was defined as the combination of participants in SLS I and II. Participants enrolled in the SLS II trial were significantly older than those in SLS I (mean ± SD age 52.3 ± 9.7 years versus 48.5 ± 12.3 years; *P* = 0.004) (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23282/abstract). The percentage of participants classified as dcSSc and lcSSc was comparable in the 2 trials (59% dcSSc versus 41% lcSSc in SLS I and II). The baseline mean disease duration (defined as the first sign or symptom other than Raynaud's phenomenon) was statistically shorter in SLS II compared to SLS I (mean ± SD 2.6 ± 1.8 years versus 3.2 ± 2.1 years; *P* = 0.01), and a greater percentage of participants had a disease duration ≤24 months in SLS II (n = 70 [50%]) versus SLS I (n = 53 [33%]) (*P* = 0.003). The mean ± SD baseline MRSS score was comparable in the 2 trials: 14.8 ± 10.9 in SLS I and

14.7 ± 10.5 in SLS II (P = 0.89). In participants classified as dcSSc, the baseline MRSS in SLS I versus SLS II was similar (mean ± SD 21.0 ± 9.8 in SLS I versus 20.8 ± 9.4 in SLS-II; P = 0.85) (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23282/abstract).

<<hd3>>**Impact of MMF and CYC on MRSS in SLS II over 24 months.** In the SLS II participants, we compared MRSS scores at 6, 12, 18, and 24 months with those at baseline. Mean ± SD baseline MRSS scores were similar for CYC and MMF (14.0 ± 10.6 units and 15.3 ± 10.4 units, respectively). In lcSSc, the mean ± SD MRSS was 5.8 ± 3.6 units and in the dcSSc group it was 20.9 ± 9.6 units at baseline. Using observed data, there was a statistically significant decline (indicating improvement) in MRSS at all followup visits, compared to baseline ($P \leq 0.05$), both for the dcSSc and lcSSc subgroups combined and the dcSSc subgroup separately, but there was no difference between the 2 treatment arms at any followup evaluation (Figure 1**)**.<<F1>> There was also a trend for improvement in the lcSSc subgroup over a 24-month period, but this did not achieve statistical significance (data not shown**)**. The frequency distribution of observed skin changes at 24 months from baseline showed an improvement in MRSS in each cutaneous subgroup: lcSSc (CYC 64% and MMF 61.1% improvement) and dcSSc (CYC 85.2% and MMF 77.7% improvement) (Figure 2).<<F2>>

<<hd3>>**Comparing the improvement in MRSS in the SLS I versus SLS II cohorts at 6, 12, 18, and 24 months.** No significant differences in baseline MRSS were found in comparisons of dcSSc participants in the CYC arm of SLS I (21.6), the pooled MMF and CYC arms of SLS II (20.8), the pooled CYC arms from SLS I and II (21.1), the MMF arm of SLS II (21.0) and the placebo arm of SLS I (20.4) (Table 1).<<T1>> Using the linear mixed model, the changes from baseline in MRSS at 6, 12, 18, and 24 months were statistically significant within each these groups individually and pooled ($P \leq 0.05$ for each comparison). In addition, no significant differences in the changes in MRSS from baseline at 6, 12, 18, and 24 months were noted between the pooled CYC and MMF arms of SLS II and the CYC arm of SLS I ($P \geq 0.05$), but the MRSS was statistically different and improved in the treatment groups versus placebo at 12, 18, and 24 months ($P < 0.05$) (Table 1 and Figure 1).

<<hd3>>**Comparison of mRSS in SLS I placebo versus SLS I CYC and SLS II CYC and MMF in dcSSc at 12 months.** MRSS improvements exceeding the MCID (≥5.0 units) were observed in 40% of the participants in the CYC arm of SLS I, 37% of the participants in the

pooled CYC and MMF arms of SLS-II, and 38% of the participants in the MMF arm of SLS II, compared to 25% of the participants in the placebo arm of SLS I. Conversely, worse scores that exceeded the MCID for MRSS were found in only 7% of participants in the CYC arm of SLSI, 4% of the participants in the pooled CYC and MMF arms of SLS-II, and 4% of the participants in the MMF arm of SLS II, in contrast to 16% of participants in the placebo arm of SLS I (P = 0.009) (Table 2).<<T2>>

<<hd1>>**DISCUSSION**

Skin thickness is a surrogate for disease severity in patients with dcSSc, and is associated with increased risk of internal organ involvement and mortality (16). The MRSS is a feasible, reliable, and valid measure of skin thickness that has been used as the primary outcome measure in clinical trials of SSc (3,17). Herein, we utilized data from 2 randomized controlled trials to study the efficacy of CYC (in SLS I and SLS II) and MMF (in SLS II) on MRSS in comparison with placebo (in SLS I). In addition, we compared responses to these 2 active agents between patients with dcSSc and those with lcSSc subsets. We showed that both CYC and MMF led to clinically meaningful improvements in MRSS in patients with dcSSc, and the improvements were significantly larger than those observed in the placebo arm. Our data support the role of oral CYC and MMF not only for SSc-associated ILD, but also for skin improvement in participants with dcSSc.

Previous uncontrolled studies have evaluated both CYC and MMF in dcSSc. Improvement in MRSS has been demonstrated by a combination of either intravenous or oral CYC (≤2 mg/kg daily for 12 months and then maintained on ≤1 mg/kg daily), and prednisone over a 12-month period, compared to participants who received azathioprine (2.5 mg/kg daily for 12 months and then maintained on 2 mg/kg daily) in open label studies (9–11). The effectiveness of MMF in dcSSc was retrospectively investigated in a large UK cohort and was shown to be associated with an improved 5-year survival compared to other immunosuppressive therapies, whereas no significant differences in MRSS outcome were noted between those patients receiving MMF and those treated with other standard immunosuppressive therapies: antithymocyte globulin (32.1%), azathioprine (18.3%), intravenous CYC, and MTX (14.7% each) (12). The effectiveness of MMF on dcSSc was further studied in a US scleroderma center

(13), and the change in MRSS from baseline was calculated at 3-month intervals up to 12 months. The results were compared to those observed in a historical control group derived from a pooled analysis of 3 large multicenter randomized clinical trials (1). A significant improvement in MRSS compared with baseline was detected at 6 and 9 months, and this effect was maintained throughout the 12-month followup period. There was no statistical significance achieved at 6 months in mean ± SD MRSS between MMF and the historical controls (MMF −3.05 ± 7.4 versus recombinant relaxin −4.83 ± 6.99; $P = 0.059$), but was significantly lower at 12 months (MMF −7.59 ± 10.1 versus D-penicillamine −2.47 ± 8.6; $P < 0.001$ and versus oral collagen −3.4 ± 7.12; $P = 0.002$) (13).

Our current post hoc analysis supports the results of case series and uncontrolled trials showing that both CYC and MMF are efficacious in early dcSSc, and that MMF appears to be better tolerated than oral CYC (8), findings that further support the increasing use of MMF for the management of SSc (12,18). However, the choice of the therapy depends on physician preferences and resources available in each health care system. In addition, significant improvement in MRSS compared to baseline was observed mainly beyond 6 months of treatment, an important point to consider when designing a clinical trial in SSc, as a shorter trial duration can yield a negative result using the traditional immunosuppressives. This may not be applicable for novel targeted therapeutics.

Our study has several strengths. It utilized 2 large SSc randomized controlled trials in which MRSS measurements were captured at regular intervals and performed by experienced researchers in SSc. The study is not without limitations. First, our study is a pooled, post hoc analysis. Both studies were designed primarily to evaluate the impact of treatment on ILD in patients with SSc-associated ILD, and only secondarily to assess the effect of therapy on MRSS. Second, there were missing data, and a few of the participants did not have MRSS measurements at each followup. However, we used linear mixed model to account for this.

In conclusion, our data further support the role of MMF and CYC in the improvement in skin thickness in patients with SSc. In the SLS II trial, 2 years of daily MMF and 1 year of CYC were each associated with clinically meaningful and statistically significant improvements in MRSS versus placebo arm in patients with dcSSc over a 24-month period.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Khanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Namas, Tashkin, Furst, Wilhalme, Roth, Kafaja, Volkmann, Clements, Khanna.

Acquisition of data. Namas, Tashkin, Furst, Kafaja, Clements, Khanna.

Analysis and interpretation of data. Namas, Tashkin, Furst, Wilhalme, Tseng, Roth, Kafaja, Volkmann, Clements, Khanna.

<<hd1>>**REFERENCES**

<<ref1>>

1. Amjadi S, Maranian P, Furst DE, Clements PJ, Wong WK, Postlethwaite AE, et al. Course of the modified Rodnan skin thickness score in systemic sclerosis clinical trials: analysis of three large multicenter, double-blind, randomized controlled trials. Arthritis Rheum 2009;60:2490–8.
2. Clements P, Lachenbruch P, Siebold J, White B, Weiner S, Martin R, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995;22:1281–5.
3. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387:2630–40.
4. Pope JE, Bellamy N, Seibold JR, Baron M, Ellman M, Carette S, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum 2001;44:1351–8.
5. Van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24-week randomized double-blind trial, followed by a 24-week observational trial. Br J Rheumatol 1996;35:364–72.

6. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.
7. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006;54:3962–70.
8. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708–19.
9. Domiciano DS, Bonfa E, Borges CT, Kairalla RA, Capelozzi VL, Parra E, et al. A long-term prospective randomized controlled study of non-specific interstitial pneumonia (NSIP) treatment in scleroderma. Clin Rheumatol 2011;30:223–9.
10. Pakas I, Ioannidis JP, Malagari K, Skopouli FN, Moutsopoulos HM, Vlachoyiannopoulos PG. Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. J Rheumatol 2002;29:298–304.
11. Nadashkevich O, Davis P, Fritzler M, Kovalenko W. A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. Clin Rheumatol 2006;25:205–12.
12. Nihtyanova SI, Brough GM, Black CM, Denton CP. Mycophenolate mofetil in diffuse cutaneous systemic sclerosis: a retrospective analysis. Rheumatology (Oxford) 2007;46:442–5.
13. Le EN, Wigley FM, Shah AA, Boin F, Hummers LK. Long-term experience of mycophenolate mofetil for treatment of diffuse cutaneous systemic sclerosis. Ann Rheum Dis 2011;70:1104–7.
14. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007;176:1026–34.

15. Khanna D, Furst DE, Hays RD, Park GS, Wong WK, Seibold JR, et al. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. Ann Rheum Dis 2006;65:1325–9.
16. Clements PJ, Hurwitz EL, Wong WK, Seibold JR, Mayes M, White B, et al. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. Arthritis Rheum 2000;43:2445–54.
17. Khanna D, Merkel PA. Outcome measures in systemic sclerosis: an update on instruments and current research. Curr Rheumatol Rep 2007;9:151–7.
18. Nagaraja V, Denton CP, Khanna D. Old medications and new targeted therapies in systemic sclerosis. Rheumatology (Oxford) 2015;54:1944–53.

<<</ref1>>

APPENDIX A: PARTICIPANTS IN THE SCLERODERMA LUNG STUDY I AND MEMBERS OF THE SCLERODERMA LUNG STUDY II RESEARCH GROUP

Participants in the Scleroderma Lung Study I were D. Khanna (University of Michigan, Ann Arbor); P. J. Clements, D. P. Tashkin, R. Elashoff, J. Goldin, M. Roth, D. Furst, K. Bulpitt, W.-L. J. Chung, S. Viasco, M. Sterz, L. Woolcock, X. Yan, J. Ho, S. Vasunilashorn, I. da Costa (University of California, Los Angeles); J. R. Seibold, D. J. Riley, J. K. Amorosa, V. M. Hsu, D. A. McCloskey, J. E. Wilson (University of Medicine and Dentistry of New Jersey, New Brunswick); J. Varga, D. Schraufnagel, A. Wilbur, D. Lapota, S. Arami, P. Cole-Saffold (University of Illinois, Chicago); R. Simms, A. Theodore, P. Clarke, J. Korn, K. Tobin, M. Nuite (Boston University, Boston, Massachusetts); R. Silver, M. Bolster, C. Strange, S. Schabel, E. Smith, J. Arnold, K. Caldwell, M. Bonner (Medical University of South Carolina, Charleston); R. Wise, F. Wigley, B. White, L. Hummers, M. Bohlman, A. Polito, G. Leatherman, E. Forbes, M. Daniel, D. Martin (Johns Hopkins University School of Medicine, Baltimore, Maryland); V. Steen, C. Read, C. Cooper, S. Wheaton, A. Carey, A. Ortiz (Georgetown University, Washington, DC); M. Mayes, E. Parsley, S. Oldham, T. Filemon, S. Jordan, M. Perry (University of Texas, Houston); K. Connolly, J. Golden, P. Wolters, R. Webb, J. Davis, C. Antolos, C. Maynetto (University of California, San Francisco); B. Fessler, M. Olman, C. Sanders, L. Heck, T. Parkhill (University of Alabama, Birmingham); N. Rothfield, M. Metersky, R. Cobb, M. Aberles, F. Ingenito, E. Breen (University of Connecticut Health Center, Farmington); M.

Mayes, K. Mubarak, J. L. Granda, J. Silva, Z. Injic, R. Alexander (Wayne State University, Detroit, Michigan); D. Furst, S. Springmeyer, S. Kirkland, J. Molitor, R. Hinke, A. Mondt (Virginia Mason Research Center, Seattle, Washington); T. Thompson (Harvard Medical School, Boston, Massachusetts); S. Rounds (Veterans Affairs Medical Center, Brown University, Providence, Rhode Island); M. Weinstein (Cedars Sinai Medical Center, University of California, Los Angeles); B. Thompson (Clinical Trials & Surveys, Baltimore, Maryland); and H. Paulus and S. Levy (Mortality and Morbidity Review Committee, University of California, Los Angeles).

In addition to the authors, members of the Scleroderma Lung Study II Research Group are E. Kissin, F.Y. Cheong (Boston University, Boston, Massachusetts); G. Marlis, J. Mason-Berry, P. Saffold, M. Rodriguez, L. Guzman, J. Brook, G. Ibrahim, K. Largaespada (University of California, Los Angeles); C. Fridley, M. Zulmastashvili, A. Manu, S. Moore (Georgetown University, Washington, DC); L. Hummers, G. Leatherman (Johns Hopkins University, Baltimore, Maryland); F. N. Hant, K. Gibson (Medical University of South Carolina, Charleston); M. Morrison (National Jewish Health, Denver, Colorado); H. Donnelly, C. Marlin, J. Gangar (Northwestern University, Evanston, Illinois); D. A. McCloskey (Rutgers University, New Brunswick, New Jersey); A. Eller, D. Leong, M. Lalosh, J. Obata (University of California, San Francisco); S. Arami, D. Franklin (University of Illinois, Urbana–Champaign); E. Schiopu, M. Benedict-Blue, V. Leone, J. Shaw (University of Michigan, Ann Arbor); F. Tan, M. Perry, J. Anderson, A. Saulino (University of Texas, Houston); P. Carey, M. Esplin (University of Utah, Salt Lake City); and P. Carlson (University of Minnesota, Minneapolis).

<<label>>**Figure 1.** Course of modified Rodnan Skin Score (MRSS; in absolute values) in diffuse cutaneous systemic sclerosis over a 24-month period in Scleroderma Lung Study (SLS) participants assigned to SLS I placebo, SLS I cyclophosphamide, SLS II cyclophosphamide, and SLS II mycophenolate mofetil using the observed data. The MRSS was assessed every 3 months in SLS II and every 6 months in SLS I. $P < 0.05$ at 12, 18, and 24 months between placebo group versus others, whereas $P \geq 0.05$ for the other treatments at each of the time points.

Figure 2. Frequency distribution of observed absolute changes at 24 months from baseline in modified Rodnan Skin Score (MRSS) in **A,** diffuse cutaneous systemic sclerosis (dcSSc)

participants (n = 52 cyclophosphamide [CYC] and 53 mycophenolate mofetil [MMF]) and **B,** limited cutaneous SSc (lcSSc) participants (n = 25 CYC and 18 MMF).
<</label>>

Table1. Estimated mean changes in MRSS from baseline at 6, 12, 18, and 24 months in SLS I and II in dcSSc*

	SLS I placebo			SLS I CYC			SLS I and SLS II CYC			SLS II MMF			SLS II pooled (CYC + MMF)		
	No.	**Mean (SE)**	**% chg.**	**No.**	**Mean (SE)**	**% chg.**	**No.**	**Mean (SE)**	**% chg.**	**No.**	**Mean (SE)**	**% chg.**	**No.**	**Mean (SE)**	**% chg.**
Baseline, months	46	20.4 (9.4)	NA	49	21.6 (10.3)	NA	89	21.1 (9.7)	NA	43	21.0 (8.5)	NA	83	20.8 (9.4)	NA
6	43	−2.6 (1.0)†	12.74	45	−2.6 (1.0)†	12.5	75	−2.6 (0.8)†	12.32	39	−2.5 (1.1)‡	12.86	69	−2.5 (0.8)†	11.53
12	37	−1.5 (1.1)	8.33	43	−5.1 (1.0)‡	24.53	72	−5.4 (0.8)‡	25.59	38	−5.1 (1.1)‡	24.29	66	−5.4 (0.8)‡	26.44
18	33	−3.2 (1.1)†	16.66	36	−5.7 (1.1)‡	31.94	60	−6.0 (0.8)‡	31.27	33	−6.1 (1.1)‡	30.95	58	−6.2 (0.9)‡	30.76
24	34	−3.7 (1.1)†	19.11	32	−6.3 (1.1)‡	33.33	59	−7.2 (0.8)‡	33.64	35	−6.4 (1.1)‡	30.00	62	−7.3 (0.8)‡	33.65

* Relative change (percentage) of observed (not modeled) MRSS from baseline after 6, 12, 18 and 24 months of treatment. MRSS = modified Rodnan Skin Score; SLS = Scleroderma Lung Study; dcSSc = diffuse cutaneous scleroderma; CYC = cyclophosphamide; MMF = mycophenolate mofetil; chg. = change; NA = not applicable.

† $P < 0.05$ for MRSS at followup versus baseline within each group.

‡ $P < 0.05$ for MRSS at followup versus baseline within each group; $P < 0.05$ for active treatment groups compared to SLS I placebo group.

Table 2. Comparison of MRSS in SLS I (placebo) vs. SLS I (CYC), SLS II (CYC + MMF pooled), and SLS II (MMF) in diffuse cutaneous systemic sclerosis at 12 months using MCID (defined as ≥5 units improvement and ≥5 units worsening in MRSS)*

	No.	MRSS improvement, %	MRSS worsening, %	MRSS change, %
SLS I (placebo)	63	25	16	59
SLS I (CYC)	68	40	7	53
SLS II (pooled)	113	37	4	59
SLS II (MMF)	58	38	4	59

* MRSS = modified Rodnan Skin Score; SLS = Scleroderma Lung Study; CYC = cyclophosphamide; MMF = mycophenolate mofetil; MCID = minimum clinically important difference.