Mycophenolate Mofetil versus Oral Cyclophosphamide in Scleroderma-related Interstitial Lung Disease: Scleroderma Lung Study II

WEB APPENDIX

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III. INCLUSION CRITERIA

1. Age ≥18 years.
2. The presence of either limited (cutaneous thickening distal but not proximal to elbows and knees, with or without facial involvement) or diffuse (cutaneous thickening proximal to elbows and knees, often involving the chest or abdomen) SSc as determined by ACR criteria.
3. Dyspnea on exertion (grade ≥2 on the Magnitude of Task component of the Mahler Modified Dyspnea Index).
4. FVC ≤80% of predicted at screening and ≤ 85% at baseline
5. Onset of the first non-Raynaud manifestation of SSc within the prior 84 months.
6. Presence of any ground glass opacification (any GGO) on thoracic HRCT
7. Repeat FVC at the baseline visit (Visit #2) within 10% of the FVC value measured at screening **and** ≤ 85% predicted. If these criteria are not met, a repeat FVC may be obtained within 7 days and the subject may qualify for randomization if the repeat FVC agrees within 10% of the FVC obtained at screening.

IV. EXCLUSION CRITERIA

1. FVC <45% of predicted at either screening or baseline
2. D_LCO (Hemoglobin [Hbg]-corrected) <30% of predicted and <40% of predicted when documentation of pulmonary artery pressures by echocardiogram, right heart catheterization or magnetic resonance imaging identifies clinically significant pulmonary hypertension. All participants with a D_LCO <40% predicted must have documentation of pulmonary artery pressures in order to be considered for inclusion
3. FEV_1/FVC ratio <65% at either screening or baseline
4. Clinically significant abnormalities on HRCT not attributable to SSc
5. Diagnosis of clinically significant resting pulmonary hypertension requiring treatment as ascertained prior to study evaluation or as part of a standard of care clinical assessment performed outside of the study protocol.
6. Persistent unexplained hematuria (>10 red blood cells [RBC]/hpf)
7. History of persistent leukopenia (white blood cells [WBC] <$4.0x10^3/\mu l$) or thrombocytopenia (platelet count <$150.0x10^3/\mu l$)
8. Clinically significant anemia (<10.0 g/dl)
9. Baseline liver function test (LFTs) or bilirubin >1.5 x upper normal limit, other than that due to Gilbert's disease.
10. Concomitant and present use of captopril
11. Serum creatinine >2.0mg/dl
12. Uncontrolled congestive heart failure

13. Pregnancy (documented by urine pregnancy test) and/or breast feeding
14. Prior use of oral CYC or MMF for more than 8 weeks or the receipt of more than two intravenous doses of CYC in the past.
15. Use of CYC and/or MMF in the 30 days prior to randomization.
16. Active infection (lung or elsewhere) whose management would be compromised by CYC or MMF.
17. Other serious concomitant medical illness (e.g., cancer), chronic debilitating illness (other than SSc), unreliability or drug abuse that might compromise the patient's participation in the trial
18. Current use, or use within the 30 days prior to randomization, of prednisone (or equivalent) in doses >10 mg/day.
19. If of child bearing potential (a female participant < 55 years of age who has not been postmenopausal for $\geq$ 5 years and who has not had a hysterectomy and/or oophorectomy), failure to employ two reliable means of contraception which may include surgical sterilization, barrier methods, spermicidals, intrauterine devices, and/or hormonal contraception.
20. Use of contraindicated medications (see protocol in Appendix II for interactions of MMF and CYC with other drugs).
21. Smoking of cigars, pipes, or cigarettes during the past 6 months.
22. Use of medications with putative disease-modifying properties within the past month (e.g., D-penicillamine, azathioprine, methotrexate, Potaba).

V. BASELINE, OUTCOME AND SAFETY MEASURES

1. Pulmonary Function Tests

A. Spirometry was performed at each site by either certified pulmonary function technologists (National Board of Respiratory Care) or experienced staff that meet American Thoracic Society (ATS) recommendations (2).

a. All spirometry equipment and procedures conformed to the published standards of the ATS/ERS Task Force (3,4).
b. For all acceptable maneuvers obtained on each subject at each visit, volume-time and flow-volume curves were printed, along with the numeric results, and these print-outs were sent to the Pulmonary Function Quality Control (PFQC) core facility at UCLA for central quality control monitoring.
c. Spirometry was performed at entry (screening), just prior to initiation of study medication (baseline) and every 3 months for 24 months.

B. Subdivisions of lung volume were measured by whole-body plethysmography or at one site helium dilution according to the ATS/ERS guidelines (5) and the manufacturer's instructions.

a. Reported values included The FRC, IC and VC (or FVC, ERV and VC) of three acceptable (2 in the case of helium dilution) maneuvers. The total lung capacity (TLC) was calculated as the average of the three FRC plus IC values (or average

of the three FRC-ERV values plus the largest VC).

b. Repeatability was defined as the difference between the highest and lowest FRC values divided by the mean with a target of less than 5%.
c. The largest acceptable measured SVC and the mean of the FRC values associated with the maneuvers used for calculating the mean TLC were also reported for use in analysis.
d. The PF summary form and calibration results were mailed to the PFQC core facility at monthly intervals.
e. Lung volumes were measured at baseline and every 6 months during the trial.

C. Single-breath diffusing capacity for carbon monoxide (DLCO) was performed in accordance with the ATS/ERS guidelines using equipment and testing techniques that meet ATS/ERS requirements except that a target minimum inspiratory VC or 90% of the FVC was used (6).

a. At least 2 acceptable tests that meet repeatability criteria (6) were performed and the mean DLCO value (uncorrected for hemoglobin) from acceptable measurements were reported.
b. All quality control data should were recorded in a logbook and forwarded to the PFQC core laboratory at quarterly intervals.
c. Peripheral venous hemoglobin and carboxyhemoglobin were measured using a CO-oximeter prior to performance of the DLCO test. The COHb correction was used only if the COHb was elevated.
d. DLCO was measured at screening and every 3 months for 24 months.

D. Expression of PFT results: Pulmonary function was expressed both as measured values and as a percentage of gender-specific predicted values using the regression equations of Hankinson (7) for spirometry, Crapo (8) for subdivisions of lung volume, and Neas (9) for single-breath DLCO. For spirometry, the race-specific regression equations of Hankinson (7) were used for African-Americans and Mexican-Americans. Adjustments of reference values for TLC, RV, RV/TLC, DLCO and DL/VA for African-Americans were performed using factors recommended by the ATS (10).

2. Skin Score

Skin thickness scored using the modified Rodnan measurement method (mRSS), with a maximum score of 51. Clinical assessment of skin thickness was made in each of 17 body areas with 0-3 score (0 = normal; 1= mild thickness; 2 = moderate; 3 = severe thickness). Documented coefficient of variation is 12% for intra-observer reliability and 25% for inter-observer variability (11, 12). All measurements were performed by clinicians certified in the procedure. mRSS was measured at screening and every 3 months for 24 months

3. Self-reported Questionnaires

A. Mahler modified dyspnea index: The self-administered computer-assisted version of Mahler's Baseline Dyspneic Index (BDI) was completed by the patients at the time of the baseline visit. The self-administered computer version of the Transition Dyspneic Index (TDI) was completed by the participants every 3 months thereafter. The automated versions of these instruments have been validated (13). Standardized neutral instructions for self-completion of these questionnaires was provided by the study coordinator, but the patient provided the answers independently of the study

coordinators to minimize bias.

B. **Leicester Cough Questionnaire:** This self-administered 19-item questionnaire for the quantitative assessment of symptoms of cough frequency and severity will be completed at baseline and every 3 months (14).
C. **SF-36:** The 36 item Medical Outcomes Survey (SF-36), a generic HRQOL instrument that proved to be responsive to CYC therapy in SLS I, was given to patients for self-administration during clinic visits at baseline and every 3 months.
D. **St. George's Respiratory Questionnaire:** SGRQ, a respiratory disease-specific HRQOL instrument that was originally developed for use in COPD, has more recently been validated in SSc-ILD (15), and was self-administered at baseline and every 3 months thereafter.
E. **Health assessment questionnaire modified for scleroderma:** The SHAQ was administered at baseline and every 3 months (16).
F. **Health Utilities:** Health utilities examining patient preferences to allow estimation of the usefulness of therapy from the perspective of both the patient and society. Patients answered five questions, each consisting of 5 Likert scales from "much better" [1] to "much worse" [5] at screening, baseline, and every 3 months thereafter.
G. **UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument (UCLA SCTC GIT):** A 75-item, self-reported measure assessing bowel involvement, emotional well-being, and social functioning administered at baseline, 12 months, 24 months (17).

4. **Thoracic high resolution computed tomography (HRCT)**

Thoracic HRCT was performed at baseline and at 24-months using a standardized volume acquisition protocol developed by the HRCT Core based at the University of California, Los Angeles.

A. **Scanners:** Multidetetcor CT scanners with a minimum of 8 detectors, and wherever possible 16 or 64 channels, were employed to minimize breath hold times with procedures closely followed those reported for the NIH funded SLS-I (16) and FORTE (18) clinical trials.
B. **Imaging Procedure:** The patient was imaged prone and at suspended end-inspiration (TLC). Technologists were trained to coach maximal inspiratory breath-hold from the patients and instructed them to "Take your biggest breath in until you feel your lungs are completely full, in the same way you do in the lung function laboratory, and then signal when you feel completely full and hold your breath."
C. **Imaging Data Transfer and Storage:** Image data that that had been scrubbed of protected health information in a HIPAA-compliant manner was transferred from each Clinical Center to the Radiology Core at UCLA using a dedicated server set up for this purpose. From the DICOM receiver, incoming images were transferred to an image data server protected with a network firewall in a secure manner an accessible only to linked internal work-stations.
D. **Scanner Quality Assurance (QA):** The QA program consisted of two parts: (1) Recommendations for the initial and annual scanner testing by a medical physicist as well as the establishment or continuance of an ongoing QA program, and (2) specific bi-monthly water phantom tests; in accordance with standards established by the American College of Radiology: http://www.acr.org/dyna/?doc=departments/stand_accred/standards/standards.html

E. HRCT Interpretation:

a. **Clinical:** Radiologists at each center performed a standard clinical interpretation as part of good clinical practice and a formal radiologic report was generated for the patient's medical record.

b. **Screening Criteria:** A radiologist at the SLS-II Radiology Core screened the baseline HRCT for specific abnormalities that represented potential exclusion criteria including, but are not limited: pulmonary nodules/masses, bronchiectasis, evidence of active infection, lobar or segmental collapse, and/or mediastinal/hilar mass(es) or nodes. Two dedicated SLS-II Radiology Core Investigators also determined eligibility based on whether the scan confirmed the presence of any ground glass opacity (any GGO); defined as a hazy parenchymal opacity through which normal lung markings are visible in either the presence or absence of reticular opacity or architectural distortion (except for extensive adjacent architectural distortion and honeycombing).

c. **Quantitative Imaging Analysis (QIA):** A software toolkit of image analysis routines that forms the basis of a QIA workstation was developed by the SLS-II Radiology Core and has been used previously for the objective quantitation of lung involvement in Scleroderma-related Interstitial Lung Disease (19-21). The five key steps in QIA for calculating Quantitative Lung Fibrosis (QLF) and Quantitative Interstitial Lung Fibrosis (QILD) scores are: (1) segmentation to extract regions of interest in the image, in this case the parenchyma and associated sub-regions; (2) denoising to normalize the image to reduce the variation across multi-centers; (3) calculation of important texture features; (4) classification the patterns of interstitial lung disease in each voxel (reticulation vs. not for QLF and interstitial pattern vs. normal for QILD); (5) making a ratio of the total counts of disease patterns to the total counts of voxels in parenchyma region. The disease pattern of the QLF score is fibrotic reticulation, and the disease pattern of the QILD score is all interstitial patterns, including fibrotic reticulation, ground glass, and honeycombing.

d. **Defined HRCT Outcome Measures:** The severity (extent) of lung fibrosis (reticulations), ground glass opacity (GGO) honeycombing (HC) on thoracic HRCT were measured individually and in combination (i.e. total burden of interstitial lung disease) using these previously validated QIA texture measures (20-21) and represented as the percentage of pixels within a defined ROI that were identified as exhibiting the texture measure of interest. For example, this resulted in a measure of the quantitative extent of lung fibrosis (QLF) in either the lobe of most involvement (QLF-LM) or in the whole lung (QLF-WL), and quantitative extent of interstitial lung disease (QILD) in the lobe of maximal involvement (QILD-LM) and in the whole lung (QILD-WL).

5. Safety Monitoring

A. In addition to ongoing assessments such as the medical history, physical exam, vital signs, and the clinical reading of the thoracic HRCT, laboratory assessments were included for routine safety monitoring purposes to identify known clinical complications associated with scleroderma or with either of the study drugs, CYC and MMF. Laboratory testing as described in the following list was obtained at screening, baseline, every 2 weeks for the first 2 months and then monthly for the remainder of

the 24 month study period for each patient.

B. Renal function was assessed by serum creatinine and calculated glomerular filtration rate.

C. Bladder inflammation and hematuria was assessed by routine urinalysis including microscopic cell counts.

D. Bone marrow suppression and/or infection was monitored with a complete blood count including hemoglobin, hematocrit, white blood cell count, differential count and platelet count.

E. Serum chemistries included serum albumin, ALT, AST, alkaline phosphatase, bilirubin, cholesterol, creatinine, BUN/SUN, serum glucose, serum globulin, and serum calcium were measured at screening, baseline and every 3 months for 24 months.

F. Pregnancy urine testing of female participants of child-bearing potential was carried out at study entry and at each clinic visit while the subject received study drug.

VI. BIOSPECIMENS

Biological specimens were serially collected and stored from all participating subjects as a resource for future ancillary studies addressing the underlying biology and mechanisms associated with SSc-ILD and its response to treatment. Samples stored in the Biological Specimen Repository will be available to support meritorious research proposal that are submitted to, and approved by, the Ancillary Studies Committee. For further information regarding access to specimens contact:

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Summary of specimens collected:

Type of Specimen	Time Points Collected	# of Samples or Specimens	Storage format
Plasma	Baseline, 12 mo, 24 mo	≥ 4 per time point	0.5 ml, < -70°C
Buffy coat	Baseline, 12 mo, 24 mo	≥ 2 per time point	Cell pellet, < -70°C
Serum	Baseline, 12 mo, 24 mo	≥ 4 per time point	0.5 ml, < -70°C
Purified PBMC	Baseline, 12 mo, 24 mo	≥ 2 per time point	Cryopreserved cells in LiN2
Whole Blood RNA	Baseline, 12 mo, 24 mo	≥ 2 per time point	PAXgene tube, <-70°C
Forearm (extensor surface) skin biopsy - RNA	Baseline, 24 mo	One per time point	One-half of 4 mm punch biopsy preserved in RNA*Later*, < -70°C
Forearm (extensor surface) skin biopsy – fixed/embedded	Baseline, 24 mo	One per time point	One-half of 4 mm punch biopsy. Fixed in buffered 10% formalin fixative and embedded in paraffin block.

VII. STUDY DRUGS

1. **Preparation, encapsulation and dose packaging.** All study medications including both active drugs and placebo were formulated into matching gel-caps containing active drug at doses of 25 mg and 250 mg, respectively. Study medication was prepared by the UCLA Research Pharmacy Core and included: Bottle A, CYC 25mg capsules; Bottle B, MMF 250mg capsules; and Bottle C, matching CYC/MMF placebo capsules. Study medication was allotted in a blinded, randomized fashion such that each patient randomized into the CYC arm received active CYC (Bottle A) and matching CYC/MMF placebo (Bottle C) in the first year followed by CYC/MMF placebo (Bottle C) alone in the second year. Those randomized to the MMF arm received active MMF (Bottle B) and CYC/MMF placebo, as needed, for the entire two years. The pharmacist adjusted the relative numbers of active and placebo capsules within each dose arm to deliver the required dose and maintain the study blind. Patients received single dose packages containing either 6 or 8 capsules (depending on patient weight) and were instructed to take both a morning and evening dose package each day regardless of his/her treatment assignment.

2. **Mycophenolate Mofetil (MMF):**
   - **A. Formulation:** MMF was initially donated by Roche Laboratories as 250 mg clinical-grade research capsules. After July, 2014, MMF was purchased as 500 generic tablets from Teva Pharmaceuticals, ground, and re-formulated into matching capsules by the UCLA Research Pharmacy Core.
   - **B. Administration and Titration:** MMF was administered twice daily throughout the entire 24 month study period and initiated at dose of 500 mg twice daily (1000 mg total daily dose). Dosing was increased monthly by 250 to 500 mg (per dose) according to the following schedule until the maximum tolerated dose of 1.5 mg twice daily was achieved. Dosing was held or down-titrated at any time if indicated by study criteria for safety and/or tolerability.

MMF Titration schedule

11/01/09 through 10/31/2010	11/01/10 through 01/15/15
• Month 1: 500 mg twice daily • Month 2: 1000 mg twice daily • Month 3: 1500 mg twice daily	• Month 1: 500 mg twice daily • Month 2: 1000 mg twice daily • Month 3: 1250 mg twice daily • Month 4: 1500 mg twice daily

3. **Oral Cyclophosphamide (CYC):**
   - **A. Formulation:** Generic CYC was obtained from Roxanne Laboratories, ground, and re-formulated into matching capsules as described.
   - **B. Administration and Titration:** CYC was administered once daily during the initial 12 months of the study with the second daily dosing of "study medication" containing only placebo to maintain the study blind. During the second 12 months, patients randomized to the CYC arm received only placebo for both daily doses. CYC therapy was weight-adjusted, initiated at a dose of 50 mg or 100 mg (100 mg dosing for individuals weighing $\geq$ 81 kg), and increased monthly in 25-50 mg increments according to the following schedule until a maximum dose of 1.8 to 2.3 mg/kg was

achieved. Dosing was held or down-titrated at any time if indicated by study criteria for safety and/or tolerability.

CYC Titration Schedule:

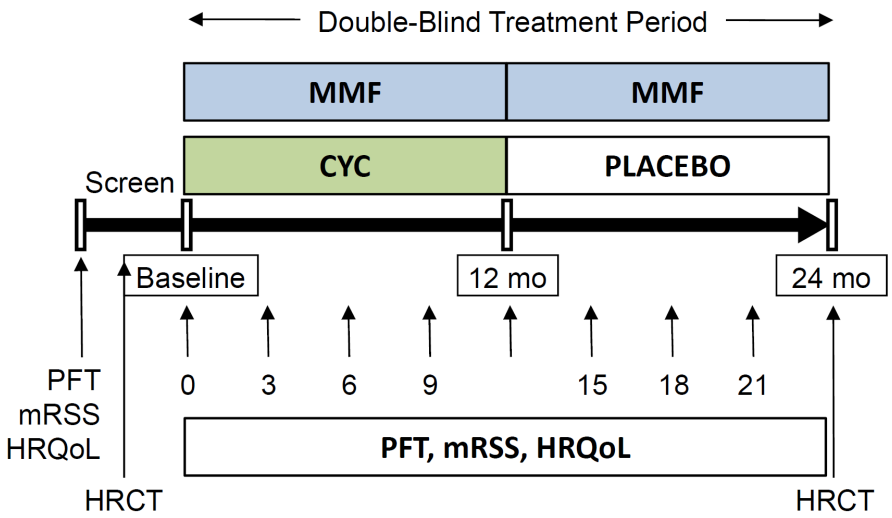
	Month 2				Month 3		
Weight (Kg)	**# CYC Capsules**	**Total CYC Dose (mg)**	**Adjusted dose (mg/kg)**		**# CYC Capsules**	**Total CYC Dose (mg)**	**Adjusted dose (mg/kg)**
43.75 to 56.24	3	75	1.3 – 1.7		4	100	1.8 – 2.3
56.25 to 68.74	4	100	1.5 – 1.8		5	125	1.8 – 2.2
68.75 to 81.24	4	100	1.2 – 1.5		6	150	1.8 – 2.2
81.25 to 93.74	5	125	1.3 – 1.5		7	175	1.9 – 2.2
93.75 to 100+	6	150	1.5 – 1.6		8	200	2.0 – 2.1

4. **Reasons for Withholding Study Drug:**
   - **A.** WBC <2500, or <1000 neutrophils
   - **B.** Platelet count <100,000.
   - **C.** Serum creatinine >2.0 mg/dl, or increase in serum creatinine of >50% over baseline, or decrease of creatinine clearance to <45 ml/min (corrected) in the absence of other etiology.
   - **D.** Hematuria with >50 RBCs/hpf, in the absence of other etiologies (i.e., urinary tract infection, renal stone, menses).
   - **E.** Malignant hypertension: BP ≥160/110 on two occasions at least 12 hrs apart, and one of the following abnormalities: proteinuria, hematuria (unrelated to menses) or casts, evidence of microangiopathic hemolytic anemia, or renal insufficiency (serum creatinine > upper limits of normal).
   - **F.** Pregnancy, or breast feeding.
   - **G.** Intractable congestive heart failure.
   - **H.** Adverse experience felt by the investigator to be clinically significant and requiring drug discontinuation.
   - **I.** Ongoing infection whose management would be significantly compromised by CYC.

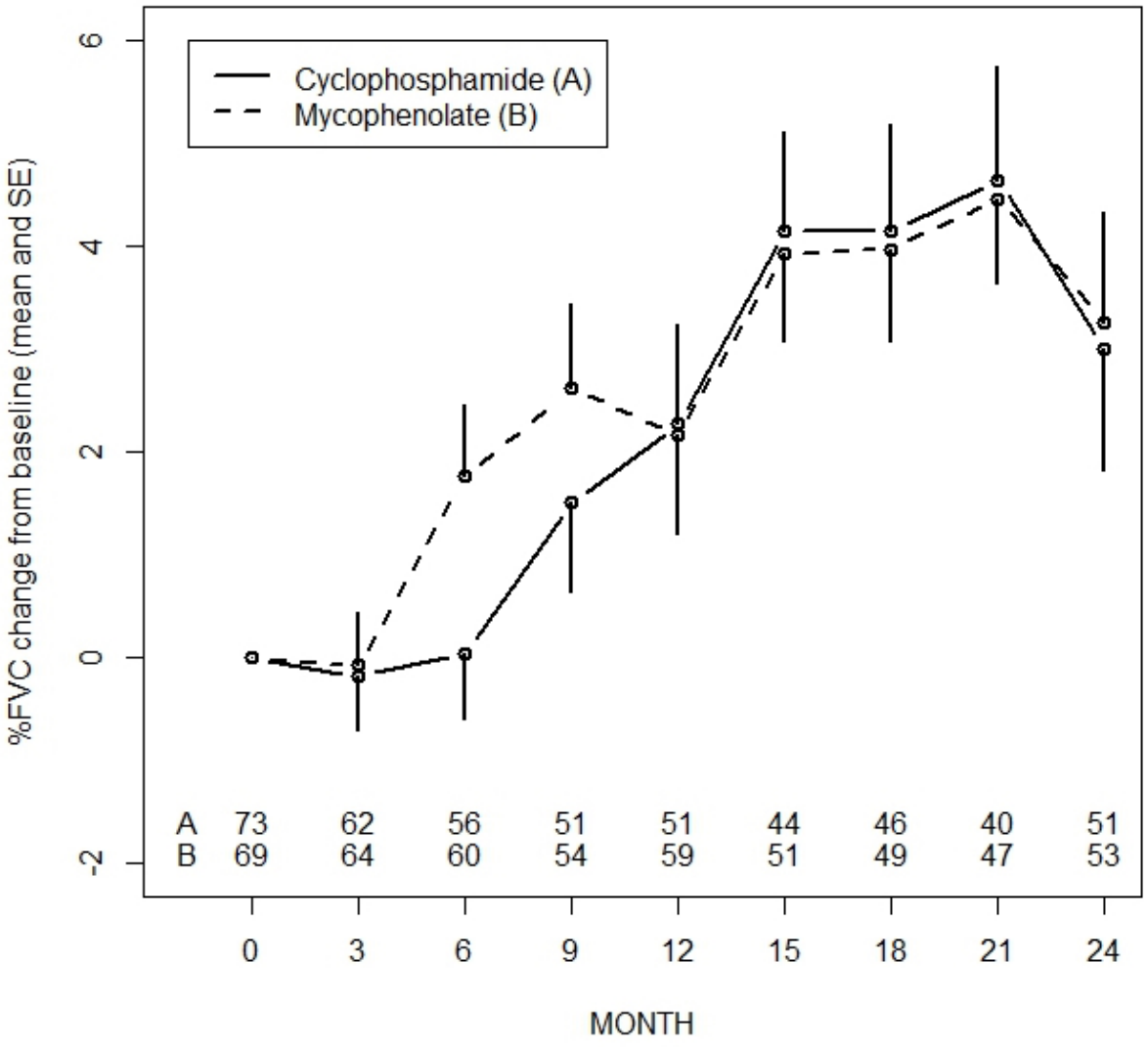
5. **Reinstitution of Study Drugs:**
   Once the reason for stopping the study drug was resolved, study drugs (MMF or CYC/Placebo) were reintroduced by starting over with the drug-specific dose titration but with the drug titration advanced ever 2 weeks (instead of every month) as tolerated. At the site investigator's discretion, after taking into account whether the study drug was likely or probably related to the adverse event, the final maintenance dose could be adjusted to either the last regular dose taken by the patient or one capsule per-dose less (500 mg/day less for MMF or 25 mg/day less for CYC). All decisions on stopping, starting and dose-titration were communicated to the Data Coordinating Center and the Pharmacy Core using pre-specified Toxicity Management Forms.

VIII. SUPPLEMENTARY FIGURES

1. Supplementary Figure 1. Overview of study design



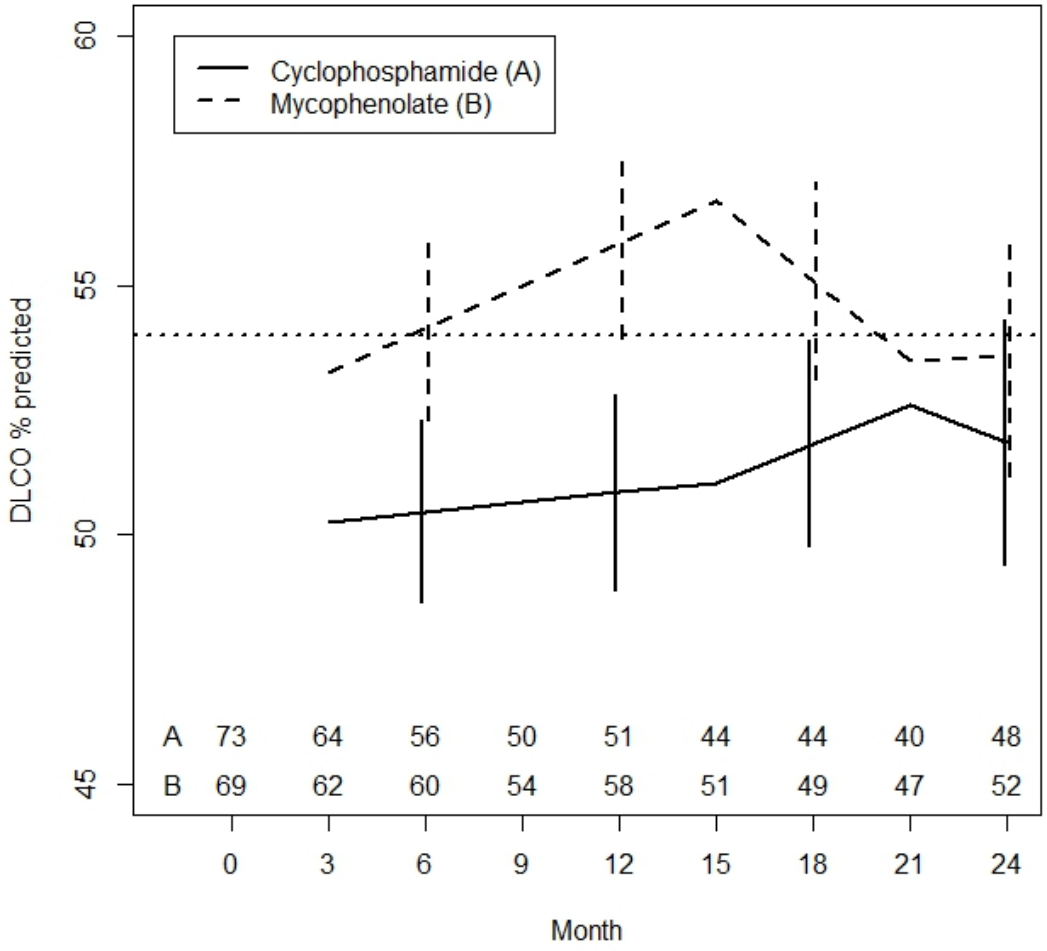
2. **Supplementary Figure 2**. **Absolute observed changes from baseline in FVC% predicted by treatment arm (all observed data, ITT). Group A=Cyclophosphamide. Group B=Mycophenolate***



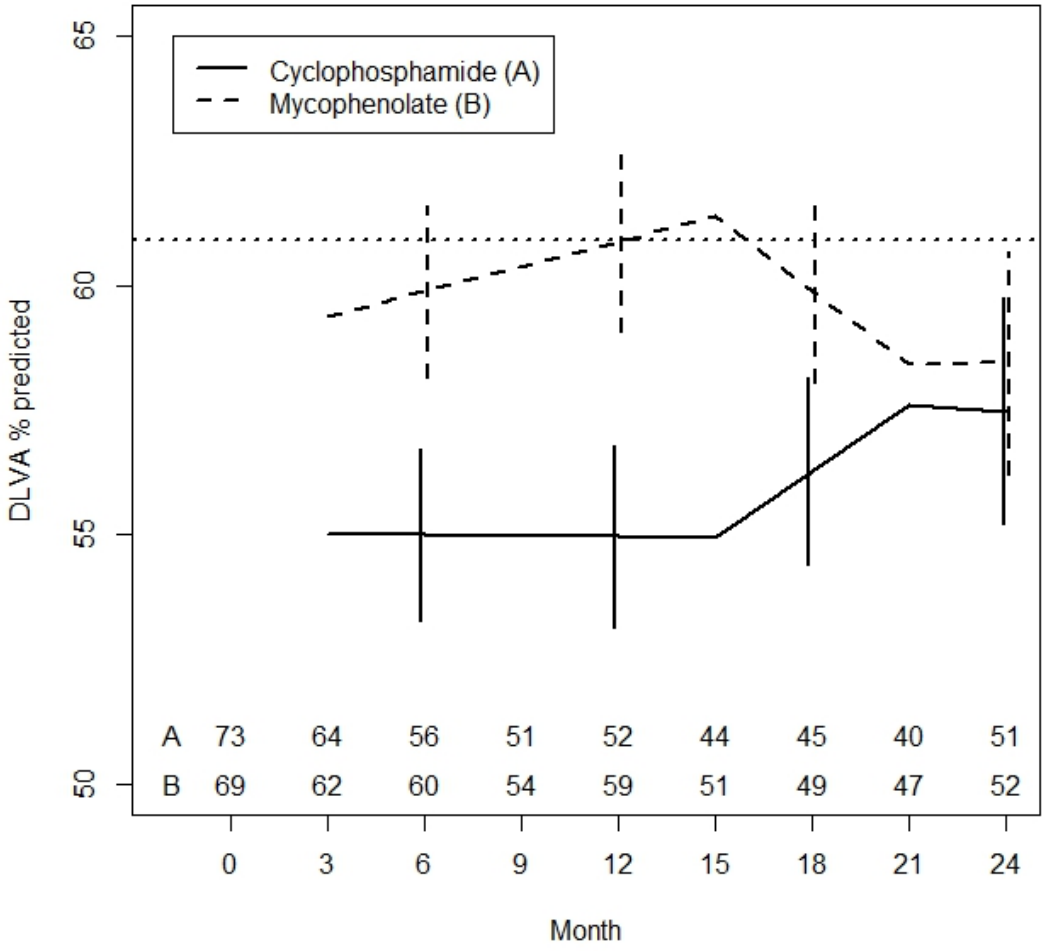
*Vertical bars represent standard error of the mean.

3. **Supplementary Figure 3**. **Absolute change in DLCO (Top Panel, A) and DL/VA (Bottom Panel, B) % predicted from baseline by treatment arm based on the joint model.**[†]

A. **DLCO %Predicted**

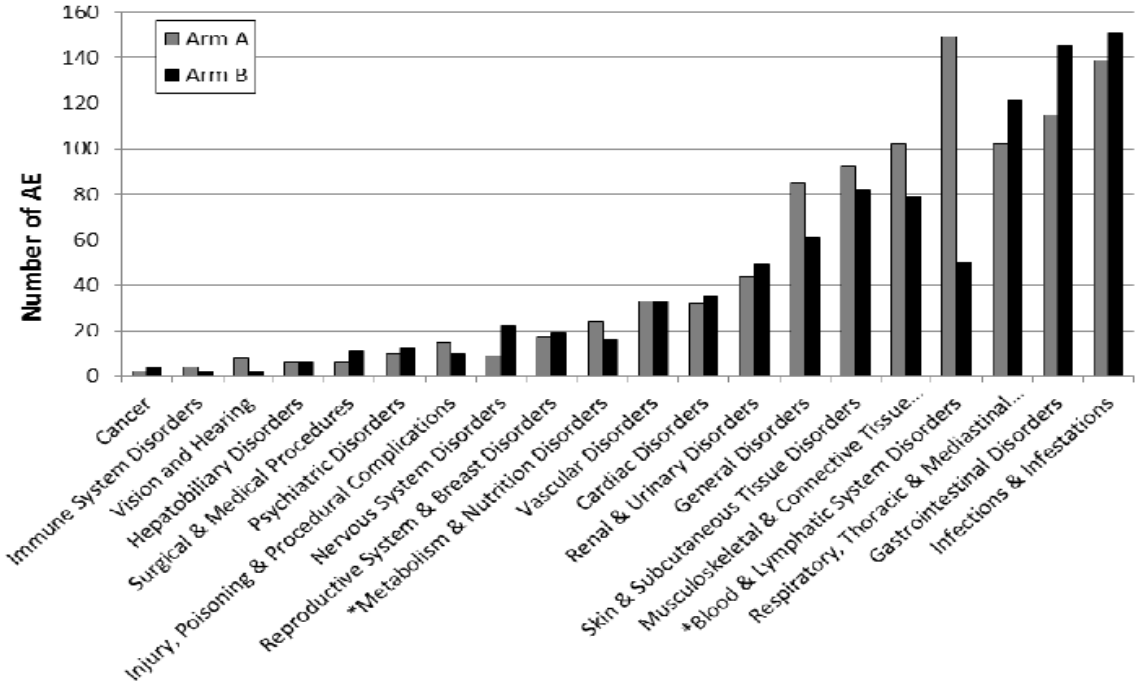


B. DL/VA %Predicted



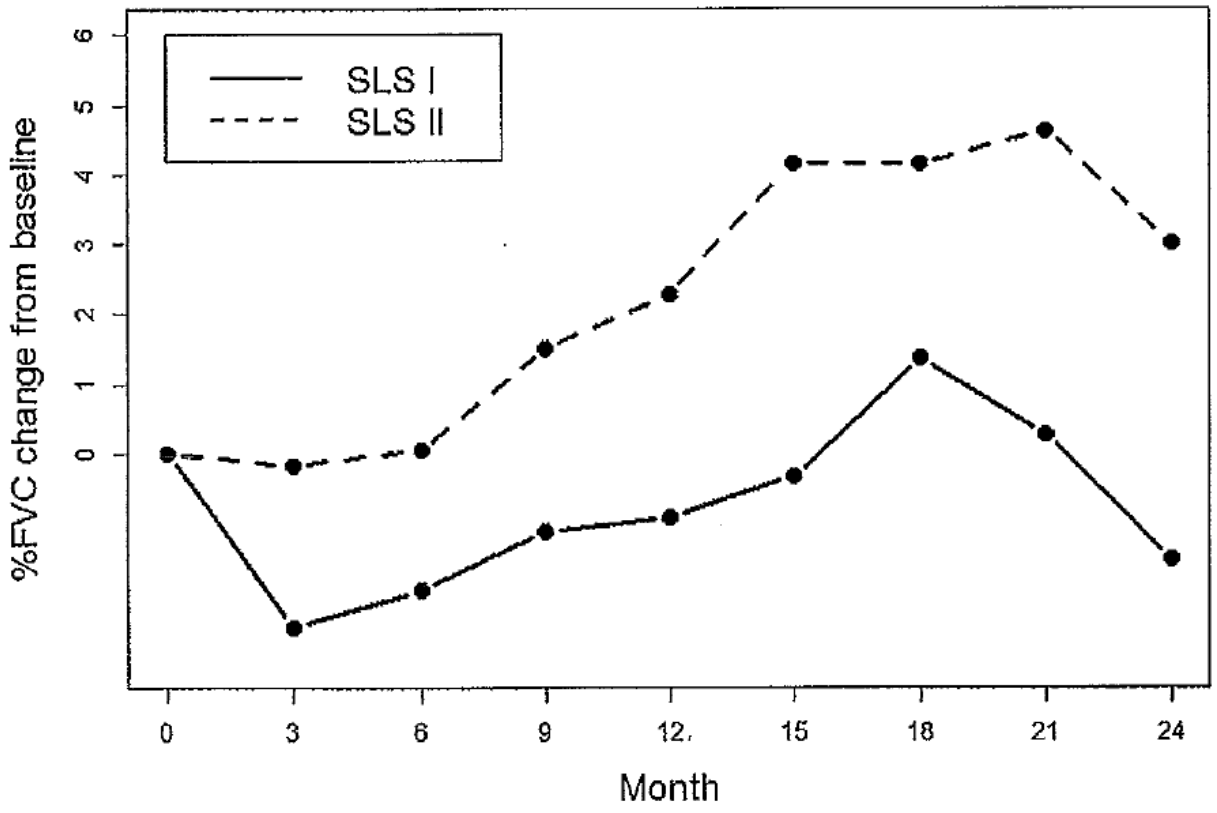
†Adjustments for baseline DLCO or DLVA % predicted, baseline HRCT lung fibrosis score and non-ignorable missing data (time to premature discontinuation of study drug, deaths and treatment failure). Vertical lines represent 95% confidence intervals. Dotted horizontal line represents the average DLCO or DLVA for both treatment arms based on the joint model (baseline values did not differ between the two treatments).

4. **Supplementary Figure 4. Adverse events according to system organ system classification by treatment arm (5A) and as pre-defined for specific protocol-directed management (5B). Arm A=Cyclophosphamide; Arm B=Mycophenolate.**

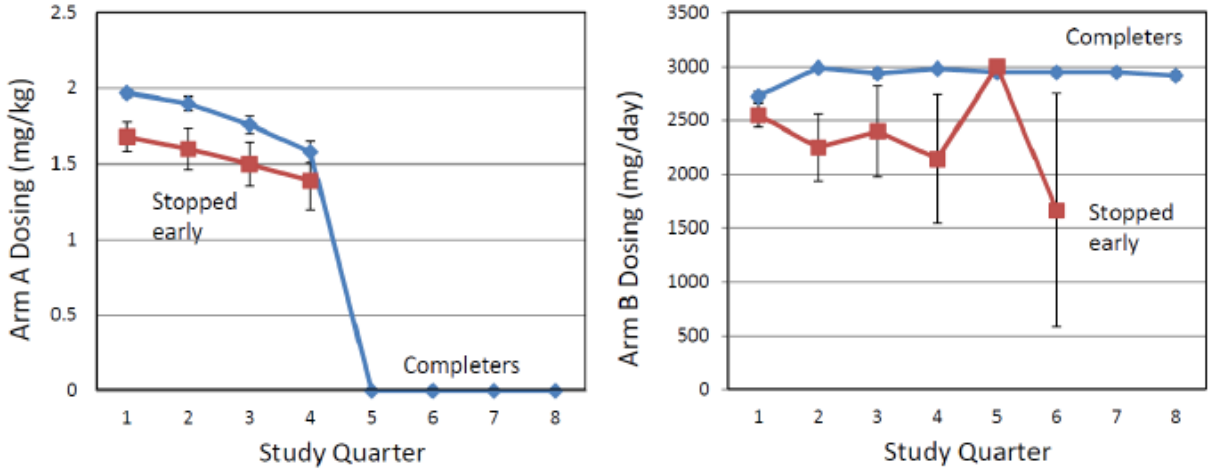


***p<0.05; Fisher's Exact Test**

5. **Supplementary Figure 5. Comparison of the changes in FVC% predicted from baseline in the CYC arm of the present trial versus the CYC arm in SLS I**



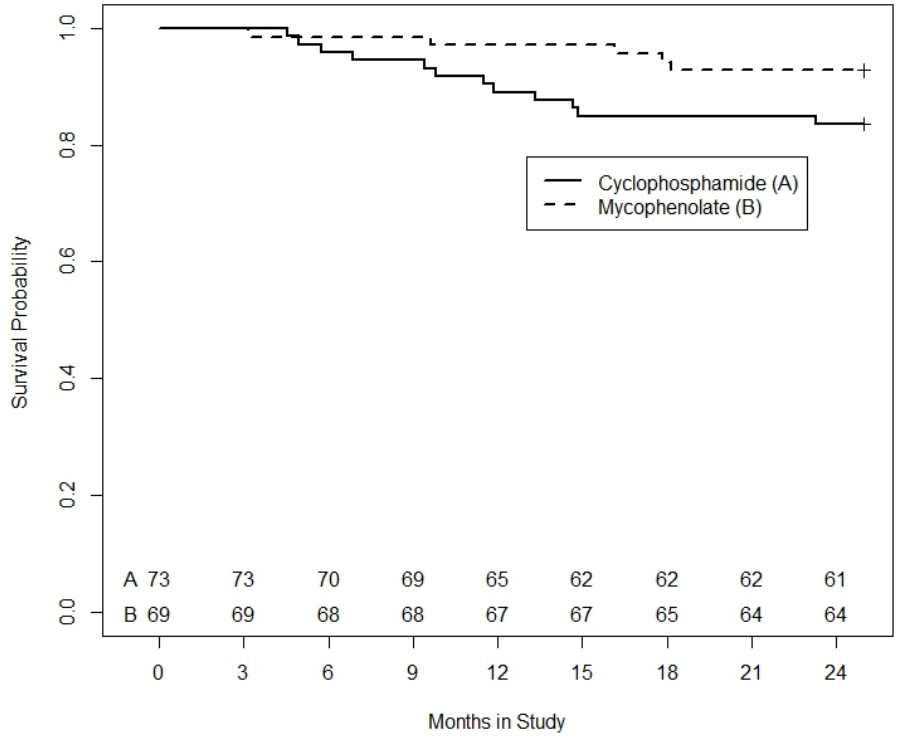
6. **Supplementary Figure 6**. **Maximum tolerated dose of each study drug during each quarter of the trial.** The time to reach the maximum targeted dose (2 mg/kg of CYC and 3 g of MMF daily) was significantly longer in the CYC arm (left panel; 152 days) than in the MMF arm (right panel; 92 days) for those who completed the study treatment



	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Comp=	37	37	37	37				
Stopped=	36	31	21	16				

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Comp=	49	49	49	49	49	49	49	49
Stopped=	20	18	10	7	4	3		

7. **Supplementary Figure 7. Time to death or treatment failure by treatment arm**



IX. SUPPLEMENTARY TABLES

1. **Supplementary Table 1.**

Reasons for premature discontinuation of study treatment (N=56).

Reason	CYC (%)	MMF (%)	Total (%)
Adverse event	15 (41.7%)	7 (35%)	22 (39.3%)
Patient request	9 (25%)	8 (40%)	17 (30.4%)
Non-compliant	6 (16.7%)	3 (15%)	9 (16.1%)
Lost to follow-up	2 (5.6%)	1 (5%)	3 (5.4%)
Death*	2 (5.6%)	1 (5%)	3 (5.4%)
Treatment failure†	2 (5.6%)	0	2 (3.6%)
TOTAL	**36 (100%)**	**20 (100%)**	**56 (100%)**

*Pertains only to deaths that occurred while subjects were still in the active treatment phase of study.

†An absolute decrease from baseline FVC of at least 15% of the predicted value occurring at least 3 months after treatment was initiated and lasting for at least one month.

2. Supplementary Table 2.

Frequency distribution of the number of subjects with the observed magnitude of change in FVC %-predicted from baseline to 24 months. [*] [†]

Results for all subjects who completed the 24-month visit (modified ITT population)

Individual subject change from baseline in absolute %-predicted FVC	CYC		MMF		Total
	N	%	N	%	
> 15	3	5.9	0	0	3
10 to 15	7	13.7	13	24.5	20
5 to 10	10	19.6	10	10.9	20
0 to 5	14	27.4	15	28.3	29
0 to -5	10	19.6	8	15.1	18
-5 to -10	5	9.8	5	9.4	10
-10 to -15	0	0	1	1.9	1
< -15	2	3.9	1	1.9	3
Total	51	49.0	53	51.0	104

*Average change in %-Predicted FVC for observed values (mean $\pm$SE):

CYC: 3.0$\pm$1.2

MMF: 3.3$\pm$1.1

[†] Positive changes represent improvement.

3. Supplemental Table 3.

Frequency distribution of the number of subjects with the observed magnitude of change in mRSS from baseline to 24 months.[*] [†]

Results for all subjects who completed the 24-month visit (modified ITT population)

Individual subject change from baseline for mRSS (points)	CYC		MMF		Total
	N	%	N	%	
5 to 7.5	1	1.89	2	3.77	3
2.5 to 5	6	11.32	5	9.43	11
0 to 2.5	4	7.55	2	3.77	6
0	3	5.66	6	11.32	9
0 to -2.5	12	22.64	7	13.21	19
-2.5 to -5	4	7.55	5	9.43	9
-5 to -7.5	7	13.21	7	13.21	14
-7.5 to -10	3	5.66	6	11.32	9
< -10	13	24.53	13	24.53	26
Total	53	50	53	50	106

*Average mRSS change (mean ±SE):

CYC: -4.74±1.04

MMF: -4.85±1.00

[†] Negative changes represent improvement.

4. Supplementary Table 4.

Frequency distribution of the number of subjects with the observed range of TDI scores at 24 months[*] [†]

Results for all subjects who completed the 24-month visit (modified ITT population). Note that the number of outcome measures is reduced, compared to other outcomes, due to problems with initiating the computer program at several sites.

Individual subject TDI Scores at 24 mo (points)	**CYC**		**MMF**		**Total**
	N	%	N	%	
> 8	3	7.69	1	2.5	4
6 to 8	6	15.38	6	15	12
3 to 5	9	23.08	9	22.5	18
1 to 2	5	12.82	3	7.5	8
0	5	12.82	5	12.5	10
-1 to -2	6	15.38	12	30	18
-3 to -5	3	7.69	2	5	5
< -5	2	5.13	2	5	4
Total	39	49.37	40	50.63	79

[*]Average TDI at 24 months:
CYC: 2.09±0.65
MMF: 1.86±0.63

[†] Positive values represent improvement.

Supplementary Table 5.

Mean changes from baseline to 24 months for study outcomes (in absolute values) with 95% confidence intervals (CI); by treatment group with between-treatment differences based on estimates from the joint model.

	CYC			MMF			ΔMMF - ΔCYC	
	N	change	95% CI	N	change	95% CI	Δ	95% CI
%-predicted FVC								
6 mo	56	0.40	-0.9 to 1.7	60	0.94	-0.4 to 2.3	0.54	-1.3 to 2.4
12 mo	51	2.10	0.60 to 3.60	59	2.31	0.84 to 3.78	0.21	-1.9 to 2.3
18 mo	46	3.16	1.69 to 4.64	49	2.54	1.12 to 3.96	-0.62	-2.7 to 1.4
24 mo	51	2.88	1.19 to 4.58	53	2.19	0.53 to 3.84	-0.70	-3.1 to 1.7
%-predicted TLC								
6 mo	56	0.11	-1.34 to 1.56	60	1.37	-0.16 to 2.85	1.26	-0.9 to 3.4
12 mo	54	0.80	-0.71 to 2.3	57	0.99	-0.51 to 2.50	0.19	-2.0 to 2.3
18 mo	46	1.49	-0.30 to 3.29	49	0.62	-1.16 to 2.39	-0.87	-3.4 to 1.6
24 mo	51	0.45	-1.43 to 2.32	53	1.24	-0.68 to 3.18	0.80	-2.0 to 3.6
%predicted DLCO								
6 mo	56	-3.54	-5.4 to -1.7	60	0.12	-1.7 to 2.0	3.67	1.1 to 6.3
12 mo	51	-3.15	-5.1 to -1.2	58	1.84	-0.08 to 3.76	4.99	2.2 to 7.8
18 mo	44	-2.17	-4.2 to -0.12	49	1.09	-0.88 to 3.06	3.26	0.41 to 6.1
24 mo	48	-2.14	-4.59 to 0.31	52	-0.40	-2.81 to 2.01	1.74	-1.6 to 5.1

Table 5 (continued)

		CYC			MMF		ΔMMF - ΔCYC	
	N	change	95% CI	N	change	95% CI	Δ	95% CI
%-predicted DL/VA								
6 mo	56	-5.90	-7.6 to -4.2	60	-1.03	-2.7 to 0.7	4.88	2.5 to 7.3
12 mo	52	-5.94	-7.7 to -4.1	59	-0.03	-1.8 to 1.8	5.90	3.4 to 8.4
18 mo	45	-4.62	-6.5 to -2.7	49	1.09	-0.88 to 3.1	3.26	0.40 to 6.1
24 mo	51	-3.43	-5.7 to -1.2	52	-2.46	-4.7 to -0.2	0.96	-2.2 to 4.1
TDI								
6 mo	50	0.32	-0.4 to 1.1	52	0.87	0.13 to 1.60	0.54	-0.5 to 1.6
12 mo	47	0.89	0.12 to 1.67	49	0.87	0.11 to 1.64	-0.02	-1.1 to 1.1
18 mo	35	1.46	0.57 to 2.40	42	0.88	-0.03 to 1.8	-0.58	-1.9 to 1.0
24 mo	39	2.16	1.14 to 3.18	40	1.77	0.75 to 2.79	-0.39	-1.8 to 1.0
mRSS All								
6 mo	58	-1.57	-2.8 to 0.3	60	-0.83	-2.0 to 0.34	0.75	-0.9 to 2.4
12 mo	55	-3.57	-4.9 to -2.0	58	-3.33	-4.7 to -2.0	0.24	-1.7 to 2.2
18 mo	47	-4.49	-5.8 to -3.2	50	-4.25	-5.5 to - 3.0	0.25	-1.6 to 2.1
24 mo	53	-5.35	-6.9 to -3.8	53	-4.90	-6.4 to -3.4	0.45	-1.7 to 2.6
mRSS Diffuse								
6 mo	30	-2.98	-4.9 to -1.0	39	-1.97	-3.7 to -0.2	1.02	-0.9 to 2.4
12 mo	28	-5.66	-7.8 to -3.5	38	-5.05	-6.9 to -3.2	0.61	-1.7 to 2.2
18 mo	25	-7.06	-9.2 to -5.0	33	-6.29	-8.1 to -4.5	0.78	-1.6 to 2.1
24 mo	27	-8.29	-10.7 to -5.9	35	-6.40	-8.5 to -4.3	1.90	-1.7 to 2.6

mRSS Limited								
6 mo	28	0.53	-0.5 to 1.6	21	0.64	-0.6 to 1.9	0.11	-1.5 to 1.7
12 mo	27	-0.59	-1.8 to 0.6	20	-0.80	-2.3 to 0.7	-0.21	-2.2 to 1.8
18 mo	22	-1.17	-2.3 to -0.0	17	-1.02	-2.5 to 0.4	0.15	-1.7 to 2.0
24 mo	26	-1.56	-3.0 to -0.1	18	-2.75	-4.6 to -0.9	-1.19	3.5 to 1.1
QLF-WL[*]	47	1.13	-1.71 to 3.98	51	2.15	-0.72 to 5.03	1.02	-2.99 to 5.03
QLF-LM[*]	47	-0.27	-1.43 to 1.69	51	0.12	-1.02 to 1.26	0.39	-1.27 to 2.05
QILD-WL[*]	47	-1.84	-5.16 to 1.46	51	-0.95	-4.1 to 2.2	0.89	-3.58 to 5.36
QILD-LM[*]	47	-2.78	-5.17 to -0.40	51	-2.51	-4.9 to -0.15	0.27	-3.09 to 3.67

[*]at 24 months

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Mycophenolate vs. Oral Cyclophosphamide in Scleroderma Interstitial Lung Disease (Scleroderma Lung Study II)

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Feinberg School of Medicine, Northwestern University	*Chicago, IL*
Georgetown University School of Medicine	*Washington, DC*
Johns Hopkins University School of Medicine and The University of Maryland	*Baltimore, MD*
Medical University of South Carolina	*Charleston, SC*
University of California, San Francisco, School of Medicine	*San Francisco, CA*
National Jewish Health / University of Colorado	*Denver, Colorado*
University of Illinois at Chicago, College of Medicine	*Chicago, IL*
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ABBREVIATIONS

Adverse Event	AE	Medical Outcomes Survey	SF-36
American College of Rheumatology	ACR	Modification of Diet in Renal Disease	MDRD
American Thoracic Society	ATS	Morbidity and Mortality Review Committee	MMRC
Bronchoalveolar lavage	BAL	National, Heart, Blood, Lung Institute	NHLBI
Baseline dyspnea index/Transition dyspnea index	BDI/TDI	National Institutes of Health	NIH
Case report form	CRF	Oral cyclophosphamide	CYC
computerized data management	CDM	Oral mycophenolate mofetil	MMF
Clinical coordinating center	CCC	Pharmaceutical Technology Lab	PTL
Computer tomography	CT	Pulmonary artery hypertension	PHT
Creatinine phosphokinase	CPK	Pulmonary function test	PFT
Data coordinating center	DCC	Randomized controlled trial	RCT
Data and Safety Monitoring Board	DSMB	Ratio of DLCO to alveolar volume	D_L/V_A
David Geffen School of Medicine at UCLA	UCLA	Ratio of residual volume to total lung capacity	RV/TLC
Diffusing capacity for carbon monoxide	D_LCO	Red blood cells	RBC
Drug Information Center	DIC	Residual volume	RV
Food and Drug Association	FDA	St. George's Respiratory Questionnaire	SGRQ
Forced expiratory volume	FEV	Scleroderma	SSc
Forced expiratory volume in 1 second	FEV_1	Scleroderma Clinical Trial Consortium	SCTC
Forced vital capacity	FVC	Scleroderma-related interstitial lung disease	SSc-ILD
Functional residual capacity	FRC	Scleroderma Health Assessment Questionnaire	SHAQ
Gastrointestinal Tract	GIT		
Glomerular filtration rate	GFR		
Good manufacturing practices	GMP		
Ground glass opacification	GGO	Scleroderma Lung Study I	SLS I
		Scleroderma Lung Study II	SLS II
Health assessment questionnaire - disability index	HAQ-DI	Serious Adverse Event	SAE
		Slow vital capacity	SVC
Hemoglobin	Hgb	Total lung capacity	TLC
Health-related quality of life	HRQoL	Thoracic gas volume	TGV
High resolution computer tomography	HRCT	Transforming growth factor-beta	TGF-β
Institutional Review Board	IRB	Volume inspired	VI
Liver function test	LFT	White blood cells	WBC

PROTOCOL SUMMARY - SCLERODERMA LUNG STUDY II

TITLE	Mycophenolate vs. Oral Cyclophosphamide in Scleroderma Interstitial Lung Disease. (Scleroderma Lung Study II)
SPONSOR	National Institutes of Health (NIH) / National Heart, Lung and Blood Institute (NHLBI)
INDICATION	Treatment of Scleroderma-related interstitial lung disease (SSc-ILD)
HYPOTHESIS	The primary hypothesis is that treatment of patients suffering from active and symptomatic SSc-ILD with a two-year course of Mycophenolate mofetil (MMF; up to 1.5 g twice daily) will be safer and more effective than treatment with a one year course of oral Cyclophosphamide (CYC: up to 2 mg/kg daily).
OBJECTIVES	**Primary Objectives are to demonstrate that:** 1. The course of Forced Vital Capacity (FVC), as a percent of the age, height, gender and ethnicity adjusted predicted value, will be better over the second year of a 24-month period in the MMF treatment group than in the CYC treatment group. 2. Toxicity in those taking MMF will be less than in those taking CYC when assessed over the entire treatment period **Secondary objectives are to demonstrate that:** 1. Other physiologic measures of lung function including Total Lung Capacity (TLC), single-breath diffusing capacity for carbon monoxide (D_LCO) and the ratio of D_LCO to alveolar volume (D_L/V_A), all assessed as %-predicted, will be better over the second year of a 24-month period in the MMF treatment group than in the CYC treatment group. 2. Fibrosis score at the end of a 24-month treatment, as measured by thoracic high resolution computerized tomography (HRCT; both visually and by newly designed computer algorithm), will be better in the MMF treatment group than in the CYC treatment group. 3. Breathlessness at the end of a 24-month treatment, as assessed by the self-administered computer-assisted version of the Mahler Modified Dyspnea Index (TDI), will be better in the MMF treatment group than in the CYC treatment group. 4. Health-related quality of life (HRQoL) at the end of 24 months, as assessed by the St. George's Respiratory Questionnaire (SGRQ) and Medical Outcomes Survey (SF-36), will be better in the MMF treatment group than in the CYC treatment group. 5. Gastrointestinal tract (GIT) symptoms at the end of 24 month treatment, as assessed by the UCLA Scleroderma Clinical Trial

	Consortium (SCTC) GIT 2.0, will be better in the MMF treatment group than in the CYC treatment group. 6. Utility (a patient-determined value measure) of therapy at the end of 24 months as assessed using a combination of the SF-36 and patient-derived measures will be better in the MMF treatment group than in the CYC treatment group. 7. Functional ability at the end of 24 months, as assessed by the Scleroderma Health Assessment Questionnaire (SHAQ), will be better in the MMF treatment group than in the CYC treatment group. 8. Skin involvement at the end of 24 months, as measured by the modified Rodnan skin thickness scores, will be better in the MMF treatment group than in the CYC treatment group. 9. Our understanding of the biology and treatment of SSc-ILD will be advanced through the collection and innovative analysis of blood and skin biopsies collected during the study.
TRIAL DESIGN	Multi-center, double-blind, parallel group, randomized controlled treatment study with a 1:1 enrollment ratio. The study will consist of two parts: 1. A Screening period to determine eligibility 2. A double-blind active treatment period. After the Screening Period (screening visit 1 and 2), eligible subjects meeting all study criteria will be randomly assigned, using a center-specific block design, to the double-blind treatment phase at a 1:1 ratio to receive either up to 1) 1.5 g MMF twice daily for 24 months or 2) 2 mg/kg CYC daily for the first 12 months followed by placebo for the second 12 months. During the treatment period subjects will be evaluated at defined clinic visits (see schedule of assessments) for both toxicity (primarily via blood and urine testing) and for efficacy (via pulmonary function testing, HRCT measures of lung fibrosis, assessment of skin and dyspnea, and the use of HRQoL questionnaires). A Data and Safety Monitoring Board (DSMB) will be appointed by the NHLBI to provide external oversight concerning the scientific integrity of the study for the duration of the clinical trial. The DSMB will meet every 6 months for the duration of the trial to review cumulative trial results and evaluate treatment for the beneficial and adverse effects.
NUMBER OF SUBJECTS	A total of 150 subjects, at least 18 years old, both male and female, including different ethnic groups, will be enrolled at 12 University clinical centers nationwide.

TARGET POPULATION

Scleroderma patients, defined by American College of Rheumatology (ACR) criteria as having either limited or diffuse cutaneous SSc, who demonstrate evidence of restrictive lung disease, symptomatic dyspnea, and active interstitial lung disease as defined by thoracic HRCT criteria.

INCLUSION CRITERIA

A staged approach to screening will be employed in which subjects are first evaluated for age, disease, symptoms and pulmonary function criteria and, if meeting these criteria, undergo screening thoracic HRCT.

Inclusion criteria at screening prior to HRCT

1. Age ≥ 18
2. The presence of either limited (cutaneous thickening distal but not proximal to elbows and knees, with or without facial involvement) or diffuse (cutaneous thickening proximal to elbows and knees, often involving the chest or abdomen) SSc as determined by ACR criteria.
3. Dyspnea on exertion (grade ≥2 on the Magnitude of Task component of the Mahler Modified Dyspnea Index).
4. FVC ≤80% of predicted at screening and ≤ 85% at baseline
5. Onset of the first non-Raynaud manifestation of SSc within the prior 84 months.

Additional inclusion criteria after completing HRCT

6. Presence of any ground glass opacification (any GGO) on thoracic HRCT
7. Repeat FVC at the baseline visit (Visit #2) within 10% of the FVC value measured at screening **and** ≤ 85% predicted. If these criteria are not met, a repeat FVC may be obtained within 7 days and the subject may qualify for randomization if the repeat FVC agrees within 10% of the FVC obtained at screening.

EXCLUSION CRITERIA

Subjects will be excluded from participation if any of the following findings are documented:

1. FVC <45% of predicted at either screening or baseline
2. D_LCO (Hemoglobin [Hbg]-corrected) <30% of predicted and <40% of predicted when documentation of pulmonary artery pressures by echocardiogram, right heart catheterization or magnetic resonance imaging identifies clinically significant pulmonary hypertension. All participants with a D_LCO <40%

predicted must have documentation of pulmonary artery pressures in order to be considered for inclusion

3. FEV_1/FVC ratio <65% at either screening or baseline
4. Clinically significant abnormalities on HRCT not attributable to SSc
5. Diagnosis of clinically significant resting pulmonary hypertension requiring treatment as ascertained prior to study evaluation or as part of a standard of care clinical assessment performed outside of the study protocol.
6. Persistent unexplained hematuria (>10 red blood cells [RBC]/hpf)
7. History of persistent leukopenia (white blood cells [WBC] $<4.0x10^3/\mu l$) or thrombo-cytopenia (platelet count $<150.0x10^3/\mu l$)
8. Clinically significant anemia (<10.0 g/dl)
9. Baseline liver function test (LFTs) or bilirubin >1.5 x upper normal limit, other than that due to Gilbert's disease.
10. Concomitant and present use of captopril
11. Serum creatinine >2.0mg/dl
12. Uncontrolled congestive heart failure
13. Pregnancy (documented by urine pregnancy test) and/or breast feeding
14. Prior use of oral CYC or MMF for more than 8 weeks or the receipt of more than two intravenous doses of CYC in the past.
15. Use of CYC and/or MMF in the 30 days prior to randomization.
16. Active infection (lung or elsewhere) whose management would be compromised by CYC or MMF.
17. Other serious concomitant medical illness (e.g., cancer), chronic debilitating illness (other than SSc), unreliability or drug abuse that might compromise the patient's participation in the trial
18. Current use, or use within the 30 days prior to randomization, of prednisone (or equivalent) in doses >10 mg/day.
19. If of child bearing potential (a female participant < 55 years of age who has not been postmenopausal for $\geq$ 5 years and who has not had a hysterectomy and/or oophorectomy), failure to employ two reliable means of contraception which may include

surgical sterilization, barrier methods, spermicidals, intrauterine devices, and/or hormonal contraception.

20. Use of contraindicated medications (see Appendix A or section 4.5 for interactions of MMF and CYC with other drugs).
21. Smoking of cigars, pipes, or cigarettes during the past 6 months.
22. Use of medications with putative disease-modifying properties within the past month (e.g., D-penicillamine, azathioprine, methotrexate, Potaba).

LENGTH OF STUDY

The trial consists of a 40 day screening period and a 24 month double-blind treatment period.

INVESTIGATIONAL DRUGS

1. **Drug:** Mycophenolate mofetil (MMF, same as CellCept®)
   Manufacturer: Roche Laboratories, Inc. (through 07/31/14) Teva Pharmaceuticals, Inc. (08/01/14 through completion)
   Administration route: Oral
   Dosing unit: 250 mg capsules.
   Dosing: up to 1.5 g twice daily for 24 months as tolerated.

2. **Drug:** Cyclophosphamide (CYC)
   Manufacturer: Roxanne Laboratories, Inc.
   Administration route: Oral
   Dosing unit: 25 mg Capsules.
   Dosing: up to 2 mg/kg once daily for 12 months as tolerated.

3. **Placebo:** Inert U.S.P. filler material
   Manufacturer: Roche Laboratories, Inc. & UCLA Pharmaceutical Technology Lab
   Administration route: Oral
   Dosing unit: Capsules
   Dosing: coordinated with CYC dosing as detailed by protocol.

STUDY ASSESSMENTS

EFFICACY

1. Pulmonary Function Testing
   - %-predicted FVC
   - %-predicted TLC

- %-predicted D_LCO
- %-predicted D_L/V_A

2. Thoracic HRCT - Fibrosis score
3. TDI
4. Rodnan skin score
5. Questionnaires
   - SHAQ
   - SGRQ
   - SF-36
   - UCLA SCTC GIT 2.0
   - Health Utilities
6. Treatment failures and deaths

SAFETY

1. Adverse and Serious Adverse Events
2. Clinical laboratory testing
   - Hematology
   - Biochemistry
   - Urinalysis
3. Predetermined drug toxicity
   - Leukopenia
   - Thrombocytopenia
   - Hematuria
4. Medical history and physical findings

BIOLOGICAL

Biological samples will be collected, processed and stored for future ancillary studies that will be carried out in a manner independent from this clinical protocol.

1. Serum
2. Plasma
3. Buffy coat
4. Peripheral blood leukocytes
5. Peripheral blood RNA
6. Skin biopsy

STATISTICAL ANALYSES:

SAMPLE SIZE

A sample size estimate of 150 subjects was calculated to detect a difference between the treatment arms of 4%-predicted FVC at 24 months, adjusted for baseline FVC and HRCT-measured fibrosis score, and for a 30% missing data rate.

PRIMARY ANALYSIS

The primary analysis will involve a robust non-Bayesian joint model for longitudinal measurements of %-predicted FVC (6 – 24 mo) and the time to treatment failure or death and the time to disease-related dropout. This joint model is capable of making valid inferences on treatment effects at the longitudinal endpoint in the presence of non-ignorable missing data in %-predicted FVC due to death and dropout.

SCHEDULE OF ASSESSMENTS **(**see **Table 1**, next page)

Table 1. Schedule of Assessments

	Months after randomization																											
	Scn	BL	0.5 ±4d	1± 4d	1.5± 4d	2± 7d	3± 10d	4± 7d	5± 7d	6± 10d	7± 7d	8± 7d	9± 10d	10± 7d	11± 7d	12± 10d	13± 7d	14± 7d	15± 10d	16± 7d	17± 7d	18± 10d	19± 7d	20± 7d	21± 10d	22± 7d	23± 7d	24± 10d
General H&P	X																											X
SSc-H&P, vitals	X						X			X			X			X			X			X			X			X
Rodnan skin score	X						X			X			X			X			X			X			X			X
Lung exam	X						X			X			X			X			X			X			X			X
Mahler Dyspnea		X								X						X						X						X
SHAQ, SF-36, SGRQ, Leicester Cough Questionnaire, SSc pain/global & Health Care Utilization, PROMIS-29		X					X			X			X			X			X			X			X			X
UCLA SCTC GIT		X														X												X
LABS:																												
CBC, plat	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chem panel	X						X			X			X			X			X			X			X			X
CPK	X						X			X			X			X			X			X			X			X
Urinalysis	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preg test·	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRCT	X*																											X
Toxicity monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PFTs:																												
Spirometry	X	X**					X			X			X			X			X			X			X			X
DLCO	X						X			X			X			X			X			X			X			X
Lung volumes		X								X						X						X						X
Blood for repository		X														X												X
Skin biopsy for repository***		X																										X
Vitamin D ***							X			X			X						X			X			X			

*To take place within 40 days of Screening Visit if meet all other inclusion criteria

** Screen and Baseline FVC value must be within 10% - repeat within 7 days if not

*** Optional – not required to undergo skin biopsy or Vitamin D sub-study in order to participate in study

· For women of childbearing potential

1. INTRODUCTION AND RATIONALE

Progressive pulmonary fibrosis occurs in approximately 40% of patients with SSc and has emerged as the leading overall cause of death (89). While the exact pathobiology of SSc-ILD remains to be elucidated, inflammatory changes in skin and lungs occur early and are usually found in conjunction with, or soon followed by, deposition of collagen and destructive tissue changes (12,93). Based on the potential linkage between inflammation and fibrosis, immunosuppressive therapy has been hypothesized to be the treatment of choice (12). In Scleroderma Lung Study I (SLS I), we enrolled 158 subjects with SSc-ILD into a randomized placebo-controlled double-blind trial to evaluate a 1-year treatment with CYC on the course of forced vital capacity (FVC) and several secondary outcomes. The primary results were published in the New England Journal of Medicine in 2006 (85), with SLS I representing the first randomized controlled trial to demonstrate that SSc-ILD responds to CYC with improvements in pulmonary function, dyspnea, skin disease, and HRQoL. However, when SLS I subjects were followed for another year after completing CYC therapy, the beneficial effects of CYC waned and were completely gone by the 24 month time-point. We recently published a detailed analysis of the 2-yr SLS I data (86). Moreover, CYC was associated with significant acute toxicity and its long-term administration is limited by the risk for developing treatment-related malignancies.

This protocol, Scleroderma Lung Study II (SLS II), describes a multi-center, double-blind, randomized controlled trial (RCT) comparing a 2-year treatment with MMF (up to 1.5 g b.i.d. target dose as tolerated) with a 1-year treatment with CYC (2 mg/kg/d target dose as tolerated for one year, followed by placebo for the second year to maintain the blind) in 150 subjects with active SSc-ILD. All participants in this study will receive a study drug, either CYC or MMF, and placebos will be given only to maintain the blind between treatment arms. The design of SLS II addresses the limitations associated with CYC. MMF, an immunosuppressive drug approved for use in organ transplantation, has been administered for up to two years to subjects with SSc-ILD in several uncontrolled pilot studies (27,45,83,89a,97). Results from these small studies suggest that MMF is both effective and safe. We hypothesize that the ability to administer MMF for two years will result in a better and more sustained improvement in SSc-ILD than can be achieved with one year of CYC and that treatment with MMF will be less toxic. Furthermore, SLS II provides a unique opportunity to improve our understanding of the biology of SSc-ILD and its response to therapy by collecting and storing serum, plasma, buffy coat, purified peripheral blood mononuclear cells, and skin biopsies that will be available for a number of innovative studies. Finally, SLS I data suggested that a new composite outcome measure may provide a more robust indication of treatment response than FVC alone and SLS II will allow us to further develop and prospectively validate this new outcome tool.

SLS II will be carried out at 12 clinical sites (see cover page) and will be managed by a Clinical Coordinating Center (CCC) and a Data Coordinating Center (DCC), both of which are located at the David Geffen School of Medicine at UCLA (hereafter referred to as UCLA). Four "cores" will also be located at UCLA, including a pulmonary function quality control core, a high-resolution computerized tomography (HRCT) core, a central research pharmacy core and a purified peripheral blood mononuclear cells sample preparation core. In addition, a central Biological Specimen Repository for storing blood components and skin biopsies for ancillary mechanistic studies will be housed at the Rheumatology Division research laboratory at the University of Texas Medical School in Houston, taking advantage of their existing SSc repository.

1.1 BACKGROUND AND SIGNIFICANCE

SSc is a devastating disease with few therapeutic options. Typically, ten-year survival is in the range of 60-70% and lung involvement is the most common cause of SSc-related mortality (79). Fifty-three percent of SSc-related deaths can be ascribed to pulmonary involvement with approximately half of these related primarily to pulmonary fibrosis (53). In reviewing the time-course of disease in a subset of SSc patients with severe restriction, Steen and colleagues (79) reported that FVC declined by 32% per year (percent-change from baseline) in the first two years of disease, by 12% per year during years 2-4, and then only by 3% annually. However, a multiple regression analysis of the SLS I cohort identified baseline FVC and the severity of fibrosis on baseline CT as the primary determinants of disease progression. In this setting, disease duration between 1-7 years was not an independent predictor (85). Steen et al. (79) also demonstrated that SSc-ILD affects patients with diffuse cutaneous SSc (cutaneous sclerosis proximal to elbows and/or knees, often the trunk, with or without face) as well as those with limited cutaneous SSc (cutaneous sclerosis distal, but not proximal, to the elbows and/or knees, with or without face) with relatively similar frequency. An analysis of subjects from SLS I demonstrated the same finding (17). The development of an effective treatment for SSc-ILD will therefore directly impact the quality and longevity of life for a high percentage of SSc patients.

1.1.1 The advantages and limitations of treating SSc-ILD with CYC. A number of immunosuppressive agents have been tested in SSc, including cyclosporine, methotrexate, chlorambucil and CYC (summarized in 44). Cyclosporine is associated with very significant renal toxicity in this population. Methotrexate has shown promise for improving fibrosis in the skin (in 2 RCTs) while chlorambucil was ineffective. Six prior uncontrolled studies evaluating CYC for its effects on lung function in SSc subjects (2,7,56,71,76,79), and one open-controlled retrospective study (94) suggested positive outcomes and set the stage for SLS I (85). In SLS I, 158 SSc subjects with dyspnea, restrictive lung disease and active alveolitis were treated with either CYC or a matched placebo for 12 months and followed for an additional 12 months off study medication using a double-blind RCT design. The main results from SLS I were published in 2006 and demonstrated for the first time, in the context of a RCT, that SSc-ILD can be treated effectively and that CYC improves both lung function (FVC and TLC) and patient-centered outcomes such as dyspnea, skin thickness, and HRQoL (85). These positive findings were for the most part recently recapitulated in a smaller trial in which 45 SSc-ILD subjects were randomized to either placebo alone or to a combination of 20 mg oral prednisolone on alternate days and six monthly infusions of CYC (600 mg/m^2) in an attempt to "induce a remission", followed by oral azathioprine 2.5 mg/kg/day (31). After adjustment for baseline FVC, the active treatment group had a favorable outcome (4.19%-predicted FVC), with a trend toward statistical significance (p=0.08).

In SLS I, while patient-centered responses and the skin thickness response to CYC were very robust, beneficial responses were not observed in all subjects and the magnitude of change in FVC was modest (~2.5% improvement at 1 year compared to placebo). CYC also resulted in significantly more adverse events than did placebo, mainly leukopenia and neutropenia, and was associated with more episodes of hematuria and pneumonia (although not statistically significant). In addition, one subject developed recurrent episodes of severe bladder hemorrhage that ultimately required surgical bladder resection. Moreover, the well-known toxicity of CYC, including an increased risk of bladder cancer and leukemia with prolonged use, constrained the duration of its administration (only 1 year in SLS I). The

importance of treatment duration has become apparent with further analysis of the SLS I data. Treatment-related benefits from 1 year of CYC persisted for up to 8-9 months after stopping therapy, with a subsequent exaggerated decrement in FVC towards levels observed in the placebo group at 2 years, as we recently reported (86).

The primary findings from SLS I therefore need to be viewed cautiously, with many of the concerns pointed out in an editorial by Martinez and McCune (50) that accompanied publication in the New England Journal of Medicine: 1) the magnitude of the average improvement in lung function was relatively limited and positive results were not observed in all subjects; 2) the improvement in patient-centered outcomes (particularly breathlessness, as measured by the nurse coordinator-administered transition dyspnea index) could have been biased as a result of effective unblinding of the nurse coordinator who was aware of some of the results of the laboratory toxicity monitoring; and 3) the benefit with respect to the primary outcome (FVC %-predicted) has been shown to wane by 24 months (12 months after discontinuation of active treatment) when more stringently examined (86). While serious adverse events did not occur at a significantly higher frequency in the CYC than the placebo group, CYC is still, in the words of Martinez and McCune (50), "arguably the most toxic immunosuppressive agent currently used to treat autoimmune diseases."

The success of CYC, as well as its limitations, has led the SLS I investigators to consider a variety of other approaches as treatments to compare with CYC. The SLS I investigators have discussed this topic at almost every monthly conference call during the last three years, as well as at group sessions held during the annual meetings of the American Thoracic Society and the American College of Rheumatology. The rationale for choosing MMF as the most promising available agent to compare with CYC in SLS II is detailed in the next section.

1.1.2 Why mycophenolate mofetil (MMF) is the drug of choice for SLS II. Although the pathogenesis of SSc is not completely understood, there appear to be three pathogenic processes that contribute to its damaging effects: 1) an obliterative/ischemic vasculopathy, 2) abnormal deposition of collagen and fibrosis, and 3) an autoimmune/inflammatory component (reviewed in 16). Based on these mechanisms, a variety of therapies that might target one or more of these pathways were considered.

Vasoactive agents: Among drugs that may treat, and possibly prevent, vascular damage, prostacyclin derivatives (i.e., iloprost, epostrostenol, treprostenil) are effective in treating the pulmonary artery hypertension (PHT) associated with SSc. However, there is no evidence to date that these agents would be effective for the vascular damage and remodeling associated with SSc-ILD. Bosentan (an endothelin-1 receptor antagonist) is also indicated for treatment of SSc related PHT (1,19,34) and a variety of studies suggested that it may also have anti-fibrotic effects (57,60). Unfortunately, recent prospective RCTs evaluating bosentan for the treatment of idiopathic pulmonary fibrosis and SSc-ILD failed to show any benefit on pulmonary function (75). Sildenafil, a phosphodiesterase-5 inhibitor, has also been approved for PHT but there is currently no evidence of clinical efficacy for the treatment of SSc-ILD. Similarly, ACE-inhibitors are thought to be effective in the vascular involvement of renal crisis but no data have been developed to suggest they would be efficacious in the pulmonary vascular disease associated with SSc-ILD. As such, none of these vascular targeting agents were considered as viable candidates for SLS II.

Anti-fibrotic agents: Therapies that might prevent or treat fibrosis such as interferon-γ, α-interferon, D-penicillamine, relaxin, anti-TGF-β, or anti-connective tissue growth factor, have been considered attractive therapeutic candidates (summarized in 44). While theoretically exciting, most have already been tested in either preliminary studies or RCT for SSc-ILD and/or idiopathic pulmonary fibrosis and found to be ineffective. While there is hope that newer derivatives might still be efficacious (e.g., newer anti-connective tissue growth factor or anti-TGF- β preparations), none are available for advanced phase clinical testing at this time.

MMF as an alternative immunosuppressive/anti-inflammatory agent: As described above, a variety of immunosuppressive agents have been evaluated as potential therapies with CYC being the only one shown to be effective in a RCT. However, there is encouraging clinical evidence supporting the use of MMF. MMF inhibits inosine monophosphate dehydrogenase and has been shown to deplete guanosine nucleotides, thereby suppressing T- and B-cell proliferation and promoting apoptosis of monocytes and other inflammatory cells. The end result is an inhibition of cell-mediated immunity and antibody formation (5,18,84). Because of its immunosuppressive properties and its favorable safety profile, MMF is indicated for the prevention of organ transplant rejection and is frequently used to treat autoimmune inflammatory conditions such as lupus nephritis. MMF has also been shown to decrease mRNA for interleukin-6 and TGF-β in renal biopsies from patients undergoing acute rejection (37). These effects are particularly relevant to SSc, in which increased TGF-β may play a central pathogenetic role. One of the hallmarks of SSc is widespread microvascular damage. The pathological features of SSc vasculopathy closely resemble the occlusive vascular lesions found in solid organ transplants and responsible for transplant rejection. It has been surmised that SSc vasculopathy shares pathogenetic pathways in common with allograft vasculopathy, and gives rise to so-called "microvascular rarefaction" (28). While neointima formation and allograft inflammatory factor (25) are clearly involved, the pathogenesis of neither allograft vasculopathy nor SSc vasculopathy is well understood. A variety of reports using animal models of organ rejection suggest that MMF may beneficially influence the course of allograft vasculopathy (73,68). Furthermore, it has been speculated that the anti-rejection efficacy of MMF may be a reflection of its ability to attenuate allograft vasculopathy (88,36). The mechanism for this putative effect is unknown. It has been surmised that the beneficial effect may be related to suppression of inflammation by MMF. Other studies indicate that MMF directly inhibits vascular smooth muscle cell hyperplasia (74) or T cell activation (33). Importantly, MMF has a direct inhibitory effect on allograft inflammatory factor, which is itself directly fibrogenic (25), drives vascular damage, and is emerging as an important mediator of vasculopathy in SSc. In addition, MMF has been shown to suppress intimal accumulation and neointimal formation (36), as well as directly inhibit collagen production (69), and may block neointimal accumulation and vascular damage in allograft vasculopathy. Although experimental evidence is still lacking, similar pathogenetic mechanisms appear to be operative in driving vascular damage in SSc patients with "microvascular rarefaction." Therefore, suppression of inflammation and allograft inflammatory factor production, microvascular smooth muscle cell proliferation and inhibition of intimal collagen accumulation may all contribute to a beneficial effect of MMF on the development of allograft vasculopathy-like small vessel vasculopathy and "microvascular rarefaction" in SSc. Of further relevance to SSc, MMF inhibits proliferation of smooth muscle cells and fibroblasts (48). The clinical relevance of the above findings to

SSc-ILD is supported by preliminary data from uncontrolled clinical studies and retrospective analyses recently published (27,45,58,83,89a,97) that suggest that MMF may be a more effective, as well as a safer, immunosuppressive therapeutic agent than CYC. The SLS Investigators concluded, as did the authors of these preliminary studies, that MMF is a promising agent for SSc-ILD and that confirmatory RCTs are warranted. Furthermore, its well-established safety profile has the potential to address the major shortcomings that have been identified with respect to the use of CYC: the inability to extend therapy for longer than one year due to increasing toxicity and cancer risk. While the dose of MMF in the above-cited studies (2 g/d) was the same dose as that recommended for prevention of renal allograft rejection and for lupus nephritis, higher doses (3 g/d) are recommended for liver transplant rejection prophylaxis and have also been used successfully for the treatment of lupus nephritis with satisfactory tolerability (27a). In the latter study, diarrhea was the most common side effect but did not lead to study withdrawal in any subject and required a dose reduction in only one subject; it was also associated with fewer adverse events than intravenous CYC (27a). Since the most effective dose of MMF for treatment of SSc-ILD has not been previously explored, we propose to escalate the dose of MMF to as high as 3 g/d, as tolerated, based on the efficacy and demonstrated safety of this dose in the lupus nephritis trial (27a).

1.2 RATIONALE FOR STUDY DESIGN

There are several important reasons to conduct SLS II. **First**, SSc is a devastating disease in which pulmonary manifestations are the most frequent cause of morbidity and mortality. Studies focused on the development of new treatments for SSc-ILD have the potential to make a significant impact on the lives of SSc patients. **Second**, the SLS investigators and the infrastructure that they have developed represent a proven and valuable resource for clinical research. The collaborative interaction between pulmonologists and rheumatologists that exists in the SLS is a unique and effective resource. **Third**, while SLS I was successful in establishing the benefits of CYC for SSc-ILD, the relatively modest effects on pulmonary function, the inability to extend the duration of treatment, and the obvious toxicity of oral CYC underscore the need for a therapeutic alternative with greater and more durable efficacy and less toxicity. MMF might well meet this need. **Fourth**, SLS II will provide an important opportunity to investigate and validate new measures of treatment response that were identified as a result of SLS I. This is likely to change the standard of care for the clinical assessment and management of SSc patients. **Fifth**, SLS II will provide biological specimens to interested and experienced investigators for ancillary mechanistic studies that could advance knowledge concerning the biology of SSc-ILD and its response to therapy.

1.2.1 Why repeat a 1-year treatment with CYC (followed by a 2nd-year of placebo) as one arm of SLS-II? SLS I was the first RCT to show that subjects with SSc-ILD can respond to an immunosuppressive therapy with improvements in lung function, dyspnea, skin thickening and HRQoL (85). As such, it established a new standard of care to which other therapies should be compared. By retaining the essential inclusion/exclusion elements from SLS I, and by repeating the same treatment with CYC, we will be able to determine whether MMF offers a therapeutic advantage without the need to include a placebo arm. In the proposed study we will focus on the course of disease during the second year, the interval during which the efficacy of a 1-year treatment with CYC wanes (see preliminary results; 86). Furthermore, this design will allow us to investigate and potentially validate novel

outcome measures that were identified during the analysis of SLS I. In addition, analysis of SLS I data has allowed us to make a few important changes to streamline and focus the protocol. In SLS I, both bronchoalveolar lavage (BAL) and HRCT were performed to assess potential subjects for the presence of "active alveolitis." However, a multivariate analysis of SLS I data failed to confirm an independent relationship between the presence and/or severity of BAL findings and the baseline-adjusted FVC, dyspnea or patient-centered measures of treatment efficacy at the end of the trial (83,85). Even in the placebo group, the presence and/or severity of a BAL-defined alveolitis (> 2% neutrophils and/or > 3% eosinophils) did not predict faster or more severe progression of lung disease when baseline FVC and fibrosis on HRCT were included as covariates (83). Almost identical conclusions were recently reported by Goh and collaborators (27b). BAL is therefore not being proposed as a baseline measure in SLS II. Instead, the finding of any ground glass opacification (GGO) on thoracic HRCT, which was present in 90% of the subjects enrolled into SLS I, will be used as an entry criterion. This should enhance recruitment, as bronchoscopy was a significant deterrent for many subjects that were otherwise interested in participating. In contrast to BAL, the two best predictors of response to CYC were 1) baseline FVC and 2) the severity of fibrosis (the worst score in any region) on HRCT. Placebo-treated subjects who had evidence of more severe fibrosis on their baseline HRCT scan had the greatest declines in FVC %-predicted over the one-year treatment period, whereas the baseline degree of fibrosis had no significant influence on the 1-year change in FVC in CYC-treated subjects, and a significant fibrosis-treatment interaction was found (p=0.009). A possible conclusion from this result is that a favorable treatment effect was most evident in those with the worst fibrotic interstitial lung disease at baseline, indicating that CYC should be used to treat advanced stage patients. However, patients with longstanding SSc (> 7 yrs) were excluded from the study and it is likely that pre-existing fibrosis in our cohort identifies a subset of subjects with relatively early SSc and active alveolitis (i.e., those at greatest risk for progressive interstitial lung disease). Using this insight we will focus SLS II on the subjects most likely to respond to treatment and have refined the allowable disease duration to ≤ 7 yrs and the maximal acceptable FVC to ≤80% predicted at screening. Adopting the essential study components from SLS I, with the refinements as stated, should enhance both recruitment and the interpretation of results with MMF, while allowing us to verify the utility of a new set of outcome measures.

1.2.2 The rationale for including several hypothesis-targeted secondary outcome measures. The most striking result from SLS I was not the magnitude of change in the primary outcome, %-predicted FVC, but the pervasive change in a variety of objective and patient-centered measures of lung function and HRQoL. SSc is a complex systemic disease and the response to CYC appears to be just as multifaceted. In order to accurately capture the full breadth of the response to immunosuppressive therapy we will therefore monitor several secondary outcomes as detailed below:

Pulmonary function tests (PFTs): The physiologic hallmarks of SSc-ILD stem from the replacement of normally-compliant alveolar tissue with a combination of inflammatory and fibrotic changes. These tissue changes increase lung recoil pressure, thereby reducing both resting and dynamic lung volumes, and disrupt the alveolar-capillary interface, thereby impairing gas transfer. As a result, the progression and/or regression of interstitial lung disease is usually associated with changes in FVC, TLC, and D_LCO. Treatment responses in SLS I included a significant placebo-adjusted improvement in both FVC and TLC, making

TLC an important secondary outcome. While there was no observed treatment-related difference in the change in D_LCO, this might have reflected the enrollment of subjects with far-advanced disease with respect to either the time since onset or severity. In SLS II, subjects will be enrolled within 84 months of disease onset (excluding the onset of Raynaud's) and the lower limit for FVC will be 45% predicted, rather than 30% predicted. Furthermore, MMF may produce greater effects than observed with CYC. As a result, we will continue to track changes in D_LCO as a secondary outcome.

Thoracic HRCT: Thoracic HRCT has documented utility as a sensitive and non-invasive means of detecting and characterizing interstitial pulmonary parenchymal abnormalities in SSc-ILD (24,30,42,54,62,66,72) and provides a more complete evaluation of lung involvement than does BAL (13). Evidence of ILD is present in up to 91% of SSc patients when evaluated by HRCT (66,72) with typical interstitial abnormalities including thickened interlobular septa, subpleural lines and parenchymal bands, architectural distortion, subpleural cysts, honeycomb lung formation and GGO (4,6,59,66,91,92). In the absence of associated airway changes (such as traction bronchiectasis, bronchiolectasis), GGO of the lung identified on HRCT corresponds to histologic evidence of alveolar inflammation in patients with chronic diffuse infiltrative lung disease (9,41,66). In this setting, GGO seems to precede the HRCT appearance of honeycombing, supporting the idea that alveolitis precedes irreversible fibrosis (67). In patients with SSc, GGO is commonly present in combination with varying degrees of interstitial pulmonary fibrosis. In these patients, the implications of GGO are less well understood. More extensive GGO on HRCT and/or interstitial architectural distortion are significantly associated with a lower D_LCO (66). Analysis of baseline HRCT scans from SLS I, and follow-up HRCT scans obtained as part of an ancillary study has demonstrated that 1) the presence and extent of fibrosis at baseline is an important and independent predictor of the rate of disease progression in subjects who received placebo, and 2) that treatment with CYC (as compared to placebo) was associated with a significant improvement in the proportion of subjects who had either stable or improved HRCT measures of fibrosis (submitted manuscript). A comparison of BAL and CT findings also identified CT abnormalities as a better predictor of response to CYC. Serial monitoring of HRCT will therefore be measured in our study to validate both its predictive role and its ability to be used as a measure of treatment response.

Symptoms and function: Dyspnea is the symptom with the greatest impact on quality of life in patients with SSc-ILD. It was measured in SLS I participants using the interviewer-administered version of the Mahler Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI), a multi-dimensional instrument for assessing breathlessness (46).

The Dyspnea Index complements physiologic indicators by providing additional information not revealed by conventional physiologic tests (46,47). The older interviewer-administered version of the BDI/TDI was very responsive to treatment of SSc-ILD with CYC in SLS-I, as indicated by an improvement of the total TDI score of 1.4 in the CYC group and a worsening of the total score by 1.5 in the placebo group, a difference (2.9 units) that is not only statistically significant ($p<0.001$) but also nearly 3-times the minimal clinically significant level of 1.0 (95). However, the positive findings in SLS I could have been biased by the fact that the interviewer (nurse coordinator) may have been unblinded to study medication through awareness of abnormal laboratory findings and adverse events likely to be attributable to CYC, as pointed out by Martinez and McCune (50). Consequently, in order to obviate potential biases that could occur from the use of the older interviewer-

administered version of the BDI/TDI, we will utilize the newer, self-administered, computer-based version of the BDI/TDI, which has been well-validated (47). The newer instrument also avoids potential problems of poor standardization that existed with the administration of the older version.

The Health Assessment Questionnaire-Disability Index (HAQ-DI) and SSc-specific Visual Analog Scales (SHAQ): The HAQ-DI with added SSc-specific visual analog scales (when it is called the SHAQ) assesses daily function in SSc patients. It correlates with cutaneous and visceral involvement in SSc in cross-sectional analyses and correlates with physiologic parameters over time (14,15,51,63,64,80). The minimally important difference for the HAQ-DI in diffuse scleroderma, using the physician's global assessment as an anchor measurement, was 0.10 to 0.14 (39). The HAQ-DI was a responsive measure in SLS I and will be used in the proposed trial.

Quality of Life and Utility measures: The St. George's Respiratory Questionnaire (SGRQ) is a respiratory disease-specific HRQoL instrument that was originally developed for use in chronic obstructive pulmonary disease (35) in which it has been found to respond well to interventions (10,11,77). More recently, the SGRQ has been used in interstitial lung disease and specifically has been validated in SSc-ILD (8). For example, in SSc-ILD, it has been shown to be correlated inversely with FVC and directly with HRCT and exercise performance. For these reasons, it will be used as an outcome variable in SLS II.

UCLA Scleroderma Clinical Trial Consortium (SCTC) GIT 2.0: UCLA SCTC GIT 2.0 is a feasible, reliable, and valid instrument to assess gastrointestinal involvement in patients with SSc (Khanna D et al EULAR 2009 [abstract]). It is a 34-item instrument with 7 multi-item scales: reflux, bloating/distention, diarrhea, fecal soilage, constipation, emotional well-being, and social functioning. Because approximately 95% of patients have GIT involvement and both MMF and CYC are associated with GI symptoms, we will utilize the instrument in SLS II. In addition, we may see a beneficial effect of either therapy on the GIT symptoms.

Health Related Quality of Life: Progressive decrements in lung function of patients with symptomatic diffuse interstitial pulmonary fibrosis are likely to be accompanied by a decline in their emotional well-being and ability to perform day-to-day activities, i.e., in their HRQoL. Conversely, if treatment of scleroderma lung disease is successful, it should result not only in favorable physiologic changes but also in a relative improvement in HRQoL, compared to the placebo-treatment condition. The 36-item medical outcomes survey-II (SF 36-II), consisting of 8 scales and two summary scores (52,81) has been selected to evaluate HRQoL in SLS II. The responses to SF 36-II are standardized to responses from the U.S. general population and recently shown to be reliable, sensitive and responsive to changes in HRQoL in subjects with SSc in SLS I (39,85).

Health Utilities: Scleroderma Pain and Global Questionnaire assess the value (desirability) of a state of health against an external metric and are used to summarize HRQoL with a single number (87). Preference-based measures serve as "quality-adjustment factors" for calculating quality-adjusted life years in decision and cost-effectiveness analyses that are used in resource allocation. The SF-6D derives preference-based scores from the SF-36 where subjects rate their current health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). It requires no additional effort by the subject and can allow one to understand the value of a therapy from a societal perspective (by computing

quality-adjusted life years). In an earlier trial with diffuse SSc, SF-6D was found to have acceptable test-retest reliability, construct validity, and was responsive to change to clinical parameters (unpublished). A recent advancement in HRQoL is estimation of minimal clinically important difference, the smallest improvement in score of a HRQoL instrument that patients perceive as beneficial or that leads to a significant change in management. Identifying a minimal clinically important difference can provide a benchmark for future clinical trials in SSc by helping researchers and clinicians understand whether differences in HRQoL scores between two treatment groups, or changes within one group over time, are meaningful (39). The impact of CYC and MMF on health utility will be specifically examined in SLS II and anchored to other objective outcome measures such as FVC, enabling one to understand what a given change in a physiologic measure (like FVC) means to the patient. Likewise the use of patient preference tools will provide greater insight into the actual impact of a therapy on the patient in terms of her/his overall health.

Health Care Utilization: SLS II provides unique opportunity to assess healthcare resources utilized in the 2 arms. The costs associated with the disease and therapy will form the numerator for the cost-effectiveness analysis. Cost-effectiveness analysis is a form of full economic evaluation where both costs and consequences of health programs or treatments are examined. In SLS II, we will examine the differences in the cost (both direct and indirect costs) and effectiveness of the therapy (assessed using quality-adjusted life years from health utilities).

1.2.3 The development of a Biological Specimen Repository to support mechanistic-based ancillary studies. SLS I has provided tremendous insight into the baseline characteristics of patients with SSc-ILD, the natural progression of disease, and the pattern of change in pulmonary function, HRCT and patient-centered outcomes that occur in response to oral CYC (17,39,40,40a,82,85,86, with additional manuscripts submitted or in preparation). With the addition of a Biological Samples Repository, SLS II will provide an opportunity to gain similar insight into the biology and mechanisms involved in the pathogenesis of SSc-ILD and its response to immunosuppressive therapy. Serum, plasma, buffy coat, purified peripheral blood mononuclear cells and skin biopsies that are serially collected and cryopreserved in this repository will be available, after review and approval by the Executive Committee, to leading scientists interested in carrying out ancillary mechanistic studies. In addition to conventional auto-antibody typing that will be carried out by Dr. Mayes as part of our core studies, Dr. Gabrielli proposes to test serum samples for anti-platelet derived growth factor receptor autoantibodies as described in their recent New England Journal of Medicine article (6a). Dr. Silver (Medical University of South Carolina) proposes to examine samples for KL6, surfactant protein D and tenascin to follow-up on exciting preliminary results presented at the 2006 European League Against Rheumatism Conference. Robert Strieter (University of Virginia) would like to quantitate circulating fibrocytes and endothelial cells that have been linked to pulmonary fibrosis in animal models and in human studies (62a,54a). Our own group (UCLA) recently presented work on the multiplexed analysis of cytokines and chemokines in plasma and BAL samples collected from the SLS I study (2007 ATS Meeting), which will provide an important roadmap for more extensive studies using materials collected during SLS II. Finally, Dr. Varga (Northwestern University) envisions the analysis of TGF-β signatures during and following therapy using microarray approaches performed on skin biopsies. These and other studies

that utilize our repository will directly address the biology of SSc and SSc-ILD, and their responses to therapy.

2. OBJECTIVES

2.1 HYPOTHESIS

The primary hypothesis is that treatment of patients suffering from active and symptomatic SSc-ILD with a two-year course of Mycophenolate mofetil (MMF; up to 1.5 g twice daily) will be safer and more effective than treatment with a one year course of oral Cyclophosphamide (CYC: up to 2 mg/kg daily).

2.2 PRIMARY OBJECTIVES

The primary objectives of this protocol are to demonstrate that:

1. The course of Forced Vital Capacity (FVC), as a percent of the age, height, gender and ethnicity adjusted predicted value, will be better over the second year of a 24-month period in the MMF treatment group than in the CYC treatment group.
2. Toxicity in those taking MMF will be less than those taking CYC when assessed over the entire treatment period

2.3 SECONDARY OBJECTIVES

The secondary objectives of this protocol are to demonstrate that:

1. Other physiologic measures of lung function including Total Lung Capacity (TLC), single-breath diffusing capacity for carbon monoxide (D_LCO) and the ratio of D_LCO to alveolar volume (D_L/V_A), all assessed as %-predicted, will be better over the second year of a 24-month period in the MMF treatment group than in the CYC treatment group.
2. Fibrosis score at the end of a 24 month treatment, as measured by thoracic high resolution computerized tomography (HRCT; both visually and by a newly designed computer algorithm[43]) will be better in the MMF treatment group than in the CYC treatment group.
3. Breathlessness at the end of a 24 month treatment, as assessed by the self-administered computer-assisted version of the Mahler Modified Dyspnea Index (TDI), will be better in the MMF treatment group than in the CYC treatment group.
4. Health-related quality of life (HRQoL) at the end of 24 months, as assessed by the St. George's Respiratory Questionnaire (SGRQ) and Medical Outcomes Survey (SF-36), will be better in the MMF treatment group than in the CYC treatment group.
5. Gastrointestinal tract (GIT) symptoms at the end of 24 months, as assessed by the UCLA SCTC GIT 2.0, will be better in the MMF treatment group than in the CYC treatment group.
6. Utility (a patient-determined value measure) of therapy at the end of 24 months as assessed using a combination of the SF-36 and patient-derived measures, will be better in the MMF treatment group than in the CYC treatment group.

7. Functional ability at the end of 24 months, as assessed by the Scleroderma Health Assessment Questionnaire (SHAQ), will be better in the MMF treatment group than in the CYC treatment group.
8. Skin involvement at the end of 24 months, as measured by the modified Rodnan skin thickness scores, will be better in the MMF treatment group than in the CYC treatment group.
9. Our understanding of the biology and treatment of SSc-ILD will be advanced through the collection and innovative analysis of blood and skin biopsies collected during the study.

By the completion of SLS II, we will have directly addressed the limitations of CYC therapy that were identified in our follow-up analysis of SLS I and carefully evaluated the safety and efficacy of MMF as a potential first-line treatment for SSc-ILD, establishing whether it is more efficacious and/or safer than oral CYC. We will have also created a unique biological specimens repository and validated novel measures of treatment response that should provide new insight into the biology of SSc-ILD and its response to therapy.

3. STUDY DRUGS

3.1 OVERVIEW OF STUDY DRUG MANAGEMENT

The Drug Information Center (DIC), Department of Pharmaceutical Services, University of California Los Angeles (UCLA) Ronald Reagan Medical Center will serve as the central drug procurement, compounding, packaging, accountability and distribution site for all study drugs (CYC and MMF) and the placebo. The DIC will distribute numbered starter kits, each containing a one-month drug supply, in advance to the participating study sites so that subjects can initiate drug therapy immediately upon randomization. As the administration of CYC is weight-adjusted, starter kits will be identified by both a pharmacy-assigned supply number and by a weight category so that they can be matched to appropriate-sized patients. The DIC will utilize a predetermined randomization list to assign a specific starter kit to each subject upon randomization. Additional one-month supplies of study medication will be provided on an individualized basis to each patient during the initial 3 month dose titration period and, subsequently, 1-month supplies will be packaged and dispensed by the DIC for each patient as needed throughout the remainder of the study (unless interrupted for toxicity-related dose changes).

Each patient in the study will receive both a “morning dose” and an “evening dose” of study drug that will be taken daily during the course of the study. In order to maintain the blind between those randomized to CYC and those to MMF, and to avoid confusion between identical-appearing capsules containing active drug and placebo, unit dose packaging will be employed. Each unit dose package (prepared as sealed single-use bags) will contain the appropriate mixture of study drug and placebo specific for the patient and for the morning versus evening dose. Patients will be instructed to consume the entire contents of a single unit dose package for each dose. In addition to standard labeling instructions, color-coding will be used to distinguish between the morning and evening doses.

While investigational drugs will be obtained from the designated drug manufacturers, the UCLA Pharmaceutical Technology Lab (PTL) will be responsible for compounding CYC and starting 08/01/14 it will also be responsible for compounding MMF. In combination with Roche

Laboratories, Inc. the PTL will also be responsible for preparing placebo in capsule form, and for matching the size and appearance of all study capsules. The PTL is a licensed pharmacy and not a licensed manufacturer. As such it is governed by the California State Board of Pharmacy, FDA regulations, and good manufacturing practices (GMP) relating to pharmacy compounding. The FDA Modernization Act allows pharmacy compounding only in response to, or a reasonable expectation of, a prescription. Products compounded by PTL are limited to a maximum expiration date of 6 months based upon the aforementioned regulations.

The date of packaging, patient numbers and visit numbers packaged, lot number of capsules packaged, and expiration date will be recorded on the PTL log sheet. At any given point in time the UCLA Drug Information Staff can verify the contents of a patient's medication by checking the site, patient, and visit numbers against the PTL log sheet.

3.2 CYCLOPHOSPHAMIDE (CYC)

Generic 50 mg tablets of CYC manufactured in accord with FDA specifications by Roxanne Laboratories, Inc., will be ground and compounded with the appropriate inert U.S.P. filler and prepared into size 1 opaque capsules (Capsugel, Greenwood, SC) so that the final product contains 25 mg of CYC and matches all other study capsules in outward appearance. Each batch of capsules prepared is assigned a UCLA lot number and expiration date which is cross-referenced to: date of preparation, amount prepared, ingredient manufacturer's lot number(s) and expiration date(s), and formulation worksheet. A representative sample of each batch of capsules prepared is sent to an outside laboratory for content uniformity analysis.

Administration route: Oral
Dosing unit: Capsules compounded to contain 25 mg of CYC.
Dosing: up to 2 mg/kg once daily for 12 months as detailed:

Dosing of CYC will be initiated on a weight-adjusted basis with 50 mg (2 capsules) once-daily for individuals weighing up to 81.24 kg and 100 mg (4 capsules) once-daily for those weighing $\geq$ 81.25 kg. Dosing will then increase monthly by 25-50 mg increments according to a pre-specified weight-adjusted titration schedule (Table 2) until a maximum dose of 2 mg/kg once daily, rounded to the nearest 25 mg capsule, is reached as the daily treatment dose. The maximum daily dose of CYC that will be delivered is 200 mg, regardless of weight. Dosing may be held or down-titrated at any time if indicated by study criteria for safety and/or tolerability. Participants randomized to the CYC group will also receive matching placebo to blind for the MMF administration schedule (which is twice daily) during the first year, and then will receive only placebo to be taken twice daily during the second year.

Table 2: Initial Dose Titration Schedule for CYC arm:

		Month 2				Month 3		
Weight (Kg)		**# CYC Capsules**	**Total CYC Dose (mg)**	**Weight-adjusted dose (mg/kg)**		**# CYC Capsules**	**Total CYC Dose (mg)**	**Weight-adjusted dose (mg/kg)**
43.75 to 56.24		3	75	1.3 – 1.7		4	100	1.8 – 2.3
56.25		4	100	1.5 – 1.8		5	125	1.8 – 2.2

to 68.74								
68.75 to 81.24		4	100	1.2 – 1.5		6	150	1.8 – 2.2
81.25 to 93.74		5	125	1.3 – 1.5		7	175	1.9 – 2.2
93.75 to 100+		6	150	1.5 – 1.6		8	200	2.0 – 2.1

For subjects randomized to the CYC treatment arm, their unit-dose packaging of study drugs during the first year will contain the following weight-adjusted components once they reach the target dose (unless specifically modified due to toxicity):

Contents of morning unit-dose packaging for CYC arm during the first 12 months:

Weight (Kg)	# of 25 mg CYC capsules/package	# of Plac capsules/package	Total # of Capsules/package
43.75 to 56.24	4	2	6
56.25 to 68.74	5	1	6
68.75 to 81.24	6	0	6
81.25 to 93.74	7	1	8
93.75 to 100+	8	0	8

Contents of evening unit-dose packaging for CYC arm during the first 12 months:

Weight (Kg)	# of 25 mg CYC capsules/package	# of Plac capsules/package	Total # of Capsules/package
43.75 to 81.24	0	6	6
81.25 to 100+	0	6	6

As CYC will only be administered for 12 months, all patients randomized to the CYC treatment arm will receive unit-dose packaging that only contains placebo during the second year. Each patient will receive a unit-dose package containing 6 placebo capsules for the morning dose and another unit-dose package containing 6 placebo capsules for the evening dose.

3.3 MYCOPHENOLATE MOFETIL(MMF)

Mycophenolate mofetil (CellCept®, MMF) capsules will be prepared and supplied by Roche Labs, Inc., through the final lot expiration date of 07/31/14, as size 1 opaque capsules (Capsugel, Greenwood, SC). Each batch of capsules will be provided by the manufacturer with a lot number and expiration date that is cross-referenced to: date of preparation, certified contents and expiration date(s).

Starting 08/01/14, CellCept® will be replaced with generic 500 mg Mycophenolate mofetil

(MMF) tablets manufactured in accord with FDA specifications by Teva Pharmaceuticals, Inc. Generic MMF will be ground and compounded with the appropriate inert U.S.P. filler and prepared into size 1 opaque capsules (Capsugel, Greenwood, SC) so that the final product contains 250 mg of MMF and matches all other study capsules in outward appearance. Each batch of capsules prepared is assigned a UCLA lot number and expiration date which is cross-referenced to: date of preparation, amount prepared, ingredient manufacturer's lot number(s) and expiration date(s), and formulation worksheet. A representative sample of each batch of capsules prepared is sent to an outside laboratory for content uniformity analysis.

Administration route: Oral
Dosing unit: Capsules containing 250 mg MMF.
Dosing: up to 1.5 g twice daily for 24 months as detailed:

Dosing of MMF will be initiated at two capsules (500 mg) twice daily and will increase monthly according to the following schedule until a maximum dose of 1.5 g twice daily is reached as the daily treatment dose.

Month 1: 500 mg twice daily

Month 2: 1000 mg twice daily

Month 3: 1250 mg twice daily

Month 4: 1500 mg twice daily

Dosing may be held or down-titrated at any time if indicated by study criteria for safety and/or tolerability. Participants randomized to the MMF group will continue on the same treatment for the duration of the study and may receive placebo during the first year to maintain blinding, based on their weight, with patients who are randomized to the CYC arm. The total number of capsules delivered in their unit dose packaging (MMF capsules alone or in combination with placebo) will always match the number of capsules delivered to participants in the CYC arm, as noted above.

For subjects randomized to the MMF treatment arm, their unit-dose packaging of study drugs during the first year will contain the following weight-adjusted components once they reach the target dose (unless specifically modified due to toxicity):

Contents of morning unit-dose packaging for MMF arm during the first 12 months:

Weight (Kg)	# of 250 mg MMF capsules/package	# of Plac capsules/package	Total # of Capsules/package
43.75 to 81.24	6	0	6
81.25 to 100+	6	2	8

Contents of evening unit-dose packaging for MMF arm during the first 12 months:

Weight (Kg)	# of 250 mg MMF capsules/package	# of Plac capsules/package	Total # of Capsules/package
43.75 to 81.24	6	0	6
81.25 to 100+	6	0	6

As MMF will be administered for the entire 24 months, all patients randomized to the MMF treatment arm will continue to receive unit-dose packaging that contains MMF during the second year. Each patient will receive a unit-dose package containing 6 MMF capsules for the morning dose and another unit-dose package containing 6 MMF capsule for the evening dose, unless dosing has been specifically modified due to toxicity.

3.4 PLACEBO

Placebo will be manufactured by Roche Laboratories, Inc., and the UCLA PTL for the purpose of maintaining the blind between the CYC and MMF treatment arms due to the difference in dosing schedule (CYC daily and MMF twice daily) and the duration of drug administration (CYC for 12 months and MMF for 24 months). The Placebo will be prepared in a manner identical to the formulation of CYC except that it will only contain the U.S.P. filler without any active drug component. Placebo will be placed into size 1 opaque capsules (Capsugel, Greenwood, SC) to match all other study drugs.

Administration route:	Oral
Dosing unit:	Capsules compounded with inert U.S.P. filler material to match the active CYC and MMF study drugs.
Dosing:	taken to maintain the blind in the CYC and MMF treatment arms as detailed above.

3.5 DRUG ACCOUNTABILITY AND COMPLIANCE MONITORING

The UCLA PTL will be responsible for maintaining a central log sheet for each participating site that records the subject identification numbers for each randomized participant and the study drug box numbers that have been assigned and distributed to that subject. The PTL log sheet will also detail the number of capsules packaged in each unit-dose package and in each box, the expiration dates and the dates shipped. Dispensing pharmacists at each site will maintain drug accountability logs on a per subject basis. Logs will include date received from the PTL, date dispensed, subject number and visit number of medication dispensed, subject name/initials, subject medical record number, dose, amount dispensed, amount of unused study drug from the prior visit that was returned by subject, inventory balance, and dispenser's initials. After each visit, a compliance sheet will be sent back (by FAX or by online reporting) to the UCLA PTL and to the Data Coordinating Center detailing the study subject number, drug box numbers, date that boxes were dispensed to and returned by the subject, and a reconciliation of the number of unit-dose packages dispensed with each box and the number returned. Compliance will be calculated for each visit and for each subject from the information supplied in this manner.

4. INVESTIGATIONAL PLAN

4.1 STUDY OVERVIEW

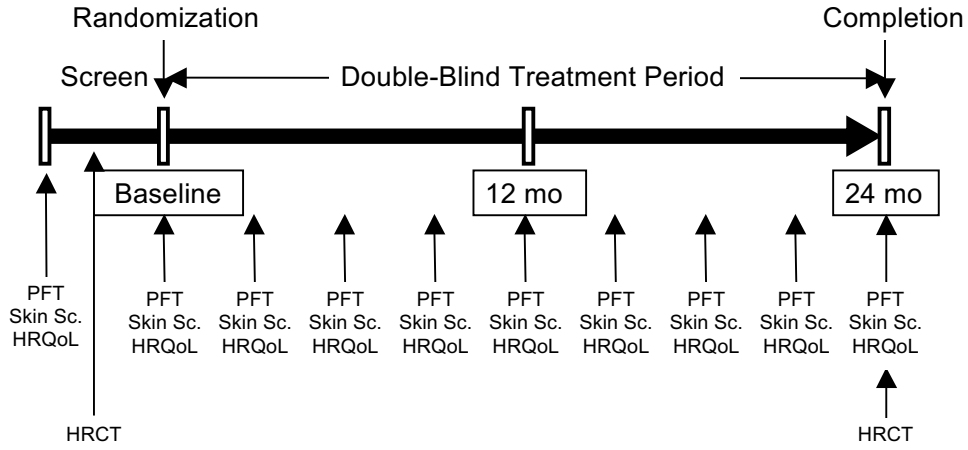
SLS II will be a 12-center, parallel-group, randomized, controlled, double-blinded study of oral MMF, up to 1.5 g twice daily (target dose as tolerated) for two years, versus oral CYC, 2 mg/kg once daily (target dose as tolerated) for one year (followed by placebo for a second year), for the treatment of active SSc-ILD. Placebos will be employed as needed to maintain the double-blind between the two treatment groups. Recruitment and management of SSc subjects will occur at the 12 clinics while the study coordination, data collection and management, drug

distribution, pulmonary function quality control and HRCT interpretation and quality control will be centralized at UCLA.

After providing written informed consent, subjects will begin a staged screening protocol in which undergoing a thoracic HRCT will be reserved for those subjects who meet all other inclusion and exclusion criteria. The HRCT will be interpreted by both the local radiologist and one of two radiologists in the central Radiology Core for both eligibility (any ground glass opacification; any GGO) and exclusion criteria (clinically significant pathology that cannot be explained by SSc such as masses, air-space consolidation, cavitary lesions, etc.). Subjects meeting HRCT criteria will then be re-assessed at a baseline visit and proceed to randomization if they demonstrate a stable baseline for the FVC (a value within 10% of the screening value, and not greater than 85% reference). If not, a repeat FVC will be obtained within 7 days and, if it agrees within 10% of the FVC at screening, the subject will proceed to randomization. Subjects failing any entry criteria will not be studied further.

Participants passing the screening process will be randomized at a 1:1 ratio, using a block design, and enter the 24 month double-blind treatment period with major outcome measures determined serially throughout the study as outlined in Figure 1 and in described in detail in **Table 1**.

Figure 1. Study Timeline and Major Study Outcome Measures



4.2 TARGET POPULATION AND TREATMENT ASSIGNMENTS

The target population is composed of men and woman of all races, at least 18 years old, who have either limited or diffuse cutaneous scleroderma, as defined by ACR criteria, and demonstrate evidence of the following three signs of active interstitial lung disease: (1) restrictive lung physiology as determined by PFT criteria, (2) symptomatic dyspnea as determined by the Mahler Modified Dyspnea Index, and (3) the presence of any GGO on thoracic HRCT imaging.

One-hundred and fifty (150) subjects will be randomized at a 1:1 ratio to the two experimental treatment arms and stratified using a block design by center and baseline FVC. One treatment arm will receive a one-year course of daily oral CYC (target dose 2 mg/kg/day as tolerated) followed by placebo in the second year and the other treatment arm will receive twice daily oral MMF (target dose 1.5 gm twice daily as tolerated) for the entire two-year treatment period. Placebo will be administered only to participants receiving CYC and only to maintain the

blind for the second daily dosing and for the second year of treatment. Randomization and treatment assignment will be verified and coordinated by the UCLA Data Coordinating Center.

4.3 INCLUSION CRITERIA

A staged approach to screening will be employed in which subjects are first evaluated for age, disease, symptoms and pulmonary function criteria and, if meeting these criteria, undergo screening thoracic HRCT and final confirmation of disease status by repeat pulmonary function testing. The numeric criteria will be applied after rounding the observed value to the number of decimal places used in the inclusion or exclusion criteria, except for age which is truncated.

4.3.1 Inclusion Criteria at screening prior to thoracic HRCT

4.3.1.1 Age $\geq$ 18

4.3.1.2 The presence of either limited (cutaneous thickening distal but not proximal to elbows and knees, with or without facial involvement) or diffuse (cutaneous thickening proximal to elbows and knees, often involving the chest or abdomen) SSc as determined by ACR criteria.

4.3.1.3 Dyspnea on exertion (grade $\geq$2 on the Magnitude of Task component of the Mahler Modified Dyspnea Index).

4.3.1.4 FVC $\leq$80% of predicted at screening and $\leq$ 85% at baseline.

4.3.1.5 Onset of the first non-Raynaud manifestation of SSc within the prior 84 months.

4.3.2 Additional Inclusion Criteria after completion of thoracic HRCT

4.3.2.1 Presence of any ground glass opacification (any GGO) on thoracic HRCT

4.3.2.2 Repeat FVC at the baseline visit (Visit #2) within 10% of the FVC measured at screening **and** $\leq$ 85% predicted. If this criterion is not met, a repeat FVC may be obtained within 7 days and the subject may qualify for randomization if the repeat FVC agrees within 10% of the FVC obtained at screening.

4.4 EXCLUSION CRITERIA

4.4.1 FVC <45% of predicted at screening or baseline

- to avoid severe, probably irreparable disease

4.4.2 DLCO (Hgb-corrected) <30% of predicted and <40% of predicted when documentation of pulmonary artery pressure(s) by echocardiogram, right heart catheterization or magnetic resonance imaging identifies clinically significant pulmonary hypertension. All participants with a DLCO <40% predicted must have documentation of pulmonary artery pressures in order to be considered for inclusion.

- to avoid severe, probably irreparable disease, or
- to avoid the presence of significant concurrent pulmonary vascular disease

4.4.3 FEV_1/FVC ratio <65% at screening or baseline

- to avoid concurrent obstructive lung disease which increases the risk for infection or the need for corticosteroid therapy
- to avoid concurrent obstructive lung disease that could alter primary and secondary outcome measures in a manner independent of the effect of the investigational drugs

4.4.4 Clinically significant abnormalities on HRCT not attributable to SSC
- e.g., lung mass, cavitary lesion, airspace consolidation, mediastinal adenopathy, etc.

4.4.5 Diagnosis of clinically significant resting pulmonary hypertension requiring treatment as ascertained prior to study evaluation or as part of a standard of care clinical assessment performed outside of the study protocol.
- to avoid concurrent scleroderma-related pulmonary vascular disease that could alter primary and secondary outcome measures in a manner independent of the effect of the investigational drugs

4.4.6 Persistent unexplained hematuria (>10 RBCs/hpf)
- to avoid pre-existing renal or bladder disease that could be exacerbated by exposure to CYC
- to avoid pre-existing renal or bladder disease that would complicate detection and treatment of one of the primary side effects of CYC therapy

4.4.7 History of persistent leukopenia (WBC <4.0 $x10^3/\mu l$) or thromboyctopenia (platelet count <150 $x10^3/\mu l$)
- to avoid pre-existing bone marrow abnormalities that could be exacerbated by exposure to CYC or MMF
- to avoid pre-existing bone marrow abnormalities that would complicate detection and treatment of one of the primary side effects of CYC and MMF therapy

4.4.8 Clinically significant anemia (<10.0 g/dl)
- to avoid pre-existing bone marrow abnormalities that could be exacerbated by exposure to CYC or MMF
- to avoid pre-existing bone marrow abnormalities that would complicate detection and treatment of one of the primary side effects of CYC and MMF therapy

4.4.9 Baseline liver function test (ALT, AST) or bilirubin >1.5 x upper normal limit, other than that due to Gilbert's disease.
- to avoid pre-existing liver disease that can alter the metabolism of CYC
- to avoid pre-existing liver disease that would complicate detection and treatment of a known side effect of MMF

4.4.10 Concomitant and present use of captopril
- to avoid its increased risk for neutropenia and thrombocytopenia which are also primary side effects of CYC and MMF

4.4.11 Serum creatinine >2.0mg/dl
- to avoid patients with scleroderma-associated renal crisis
- to avoid alterations in MMF pharmacokinetics associated with renal failure

4.4.12 Uncontrolled congestive heart failure
- to avoid unstable patients whose disease could impact on study outcomes
- to avoid patients with undiagnosed scleroderma-related heart disease

4.4.13 Pregnancy (documented by urine pregnancy test) and/or breast feeding
- contraindicated due to teratogenic effects of MMF and CYC

4.4.14 Prior use of oral CYC or MMF for more than 8 weeks or the receipt of more than two intravenous doses of CYC in the past.
- to avoid confounding effects on study outcomes

4.4.15 Use of CYC and/or MMF in the 30 days prior to randomization.
- to avoid increased risk for study associated drug toxicity

4.4.16 Active infection (lung or elsewhere) whose management would be compromised by CYC or MMF.

4.4.17 Other serious concomitant medical illness (e.g., cancer), chronic debilitating illness (other than SSc), unreliability or drug abuse that might compromise the patient's participation in the trial

4.4.18 Current use, or use within the 30 days prior to randomization, of prednisone (or equivalent) in doses >10 mg/day.
- to avoid additive risks for immunosuppression and infection
- to avoid potential for disease-modifying effects independent of study drugs

4.4.19 If of child bearing potential (a female participant < 55 years of age who has not been postmenopausal for ≥ 5 years and who has not had a hysterectomy and/or oophorectomy), failure to employ two reliable means of contraception (which may include surgical sterilization, barrier methods, spermicidals, intrauterine devices, and/or hormonal contraception).
- to avoid teratogenic effects of MMF and CYC

4.4.20 Use of contraindicated medications (see Section 4.5 and Appendix A for interactions of MMF and CYC with other drugs).

4.4.21 Smoking of cigars, pipes, or cigarettes during the past 6 months.
- to avoid risk for pulmonary complications
- to avoid impact of continued smoking and smoking cessation on study outcome measures

4.4.22 Use of medications with putative disease-modifying properties within the past month (e.g., D-penicillamine, azathioprine, methotrexate, Potaba).

A study eligibility form will be completed at the end of screening to assure that all criteria have been met before a subject is eligible for randomization.

4.5 HANDLING OF CONCURRENT MEDICATION

A number of drugs interact with the active study drugs, CYC and MMF, and therefore concurrent medications will be recorded at screening and changes in any medication recorded at each study visit. In addition, participants will be instructed to contact their study physician at the time of any medication change ordered by another physician. As this is a double-blinded study, the management of concurrent medications for all participants will be the same and the contraindications and management guidelines for both CYC and MMF will be applied to all subjects.

4.5.1 Drug-Drug Interactions related to the concurrent use of CYC. Clinically significant drug-drug interactions related to the use of CYC are listed below in **Table 3,**

including potential clinical consequences and the actions that will be taken for all participating subjects to prevent these consequences.

Table 3. CYC drug-drug interactions and management strategy

Drug	Consequence	Management
Allopurinol*	Leukopenia	Contraindicated
Amitriptyline*	↓ Serum Na	Cautionary - Use a non-tricyclic antidepressant
Amphotericin*	Renal toxicity	Contraindicated - Patients requiring amphotericin will be excluded or removed from the study
Chloramphenicol	↓ CYC effectiveness	Contraindicated - Use alternative antibiotic
Digoxin Tablets*	↓ Digoxin absorption with high dose CYC	Use Digoxin capsules or monitor digoxin levels more closely
Hydrocholorothiazide*	Leukopenia (granulocytopenia)	Use alternative diuretic or monitor CBC closely
Indomethacin*	Edema (↑ ADH secretion) and hyponatremia	Use alternative NSAID or monitor Na^+ and fluid status closely
Influenza vaccine*	Impaired immune response to vaccine	Immunize for influenza 30 days prior to CYC or administer booster
Pentostatin	Fatal cardiac toxicity	Contraindicated
Pneumococcal vaccine*	Impaired immune response to vaccine	Immunize 30 days prior to start CYC or administer booster
Ritonavir*	↑ CYC toxicity	HIV positive subjects will be excluded from study
Succinycholine	Prolonged succinycholine-induced apnea	If succinycholine needed, alert anesthesiologist, discontinue CYC during planned use of anesthesia
Tamoxifen	↑ DVT thromboembolism	Contraindicated - Patients on tamoxifen will be excluded from study
Live vaccines*	↑ likelihood of infection	Contraindicated - Avoid live vaccines

* Drugs likely to be used in this group of SSc patients on CYC. Drugs not marked have a low probability of concurrent use in this study.

4.5.2 Drug-Drug Interactions related to the concurrent use of MMF. Clinically significant drug-drug interactions related to the use of MMF are listed below in **Table 4,** including potential clinical consequences and the actions that will be taken for all participating subjects to prevent these consequences.

Table 4. MMF drug-drug interactions

Drug	Consequence	Management
Hormonal contraceptives*	Possibility of failure of contraception	Add secondary contraception with barrier/local spermicidal
Antacids (Ca, Mg, Al), Activated charcoal, Iron*	Reduces the absorption of MMF by patient	Antacids and iron should not be administered within 2 hours of the MMF dose
Acyclovir, ganciclovir, valacyclovir*	The levels of these anitvirals are increased by MMF	Monitor blood cell counts while co-administering these drugs with MMF
Cholestyramine, colesavelam, colestipol	Reduce MMF exposure by interrupting MMF enterohepatic circulation	Contraindicated - Do not co-administer these drugs with MMF
Echinacea	Reduces effectiveness of MMF	Contraindicated - Do not co-administer with MMF
Live virus vaccines (measles, mumps, polio, rotavirus, rubella, smallpox, typhoid, varicella, yellow fever)*	Inadequate immunological response to vaccine while taking an immunosuppressive drug, MMF	Avoid giving these attenuated, live virus vaccines to patients receiving MMF

* Drugs likely to be used in this group of SSc patients. Drugs not marked have a low probability of concurrent use in this study.

4.5.3 Other Contraindicated Medications. In addition to specific drug-drug interactions, additional medications may be contraindicated due to their cumulative impact on the immune system and/or to the potential for disease-modifying effects that could influence study outcomes. These medications are listed in **Table 5** below and are to be avoided as indicated during the study.

Table 5. Other Contraindicated Medications

Drug	Consequence	Management
Corticosteroids*	↑ immunosuppression leading to risk for infection	Chronic use of corticosteroids greater than 10 mg/day prednisone (or equivalent) is contraindicated. Short term use of higher doses requires increased monitoring for infections
Azathioprine	↑ immunosuppression leading to risk for infection and may have disease modifying effects	Contraindicated – do not use
Cyclosporine	↑ immunosuppression leading to risk for infection	Contraindicated – do not use
D-penicillamine	may have disease modifying effects	Contraindicated – do not use

Methotrexate	↑ immunosuppression leading to risk for infection and may have disease modifying effects	Contraindicated – do not use
Potaba	may have disease modifying effects	Contraindicated – do not use
Rituximab	↑ immunosuppression leading to risk for infection and may have disease modifying effects	Contraindicated – do not use
Etanercept	↑ immunosuppression leading to risk for infection and may have disease modifying effects	Contraindicated – do not use
Infliximab	↑ immunosuppression leading to risk for infection and may have disease modifying effects	Contraindicated – do not use
Adalimumab	↑ immunosuppression leading to risk for infection and may have disease modifying effects	Contraindicated – do not use

See **Appendix A** for more extensive list of **Table 3 – 5**

4.5.4 Drugs with narrow therapeutic windows. Drugs with narrow therapeutic windows should have close clinical follow-up with drug levels or effect monitoring during the study. This monitoring is at the discretion of the primary physician. Digoxin monitoring is noted specifically above in Table 3.

4.6 STUDY OUTCOME ASSESSMENTS

All study-related procedures and outcome measures that will be performed as part of this protocol are listed below. Specific times at which each test will be performed are summarized in **Table 1** (see end of Section 4).

4.6.1 Complete medical history and physical examination. Medical history and physical exam will be performed as per standard medical care.

4.6.2 Vital signs. Vital signs will include: pulse, blood pressure, respiratory rate, temperature (C º), height (cm), and weight (kg).

4.6.3 Pulmonary function tests (PFTs)

4.6.3.1 ***Spirometry:*** performed under the direction of the pulmonology investigator at each site and carried out by either certified pulmonary function technologists (National Board of Respiratory Care) or experienced staff that meet American Thoracic Society (ATS) recommendations (26). All spirometry equipment and procedures will conform to the most recently published standards of the ATS/ERS Task Force (55,61). Forced expiratory maneuvers will be performed at least in triplicate with the minimal

requirement that three maneuvers are "acceptable" and that two of these maneuvers meet end-of-test and repeatability criteria for FVC and FEV_1. Printouts of all data and curves will be sent to the Pulmonary Function Quality Control core facility at UCLA for central quality control monitoring (see PFT Manual of Procedures). Spirometry will be performed at entry (screening), just prior to initiation of study medication (baseline) and every 3 months for 24 months.

4.6.3.2 ***Subdivisions of lung volume:*** measured by whole-body plethysmography according to recently published ATS/ERS guideline (90) and the manufacturer's instructions. Methods of procedure will be standardized across participating centers using the same protocol that was employed in the National Emphysema Treatment Trial (NETT; see PFT Manual of Procedures). Reported values will include FRC, IC and EVC or FRC, ERV and IVC which will be used to calculate the TLC, SVC, and functional residual capacity (FRC). Lung volumes will be measured at baseline and every 6 months during the trial.

4.6.3.3 ***Single-breath diffusing capacity for carbon monoxide (D_LCO):*** performed in accordance with recently published ATS/ERS guidelines using equipment and testing techniques that meet ATS/ERS requirements (49). At least 2 acceptable tests that meet repeatability criteria (49) will be performed and the mean D_LCO value (uncorrected for Hgb) from acceptable measurements reported. Other reported values will include the inspired vital capacity (VCI; L-BTPS), which must be within 10% of the expiratory VC, and the alveolar volume (V_A; L-BTPS). D_LCO will be measured at the screening visit, and every 3 months for 24 months.

4.6.3.4 ***Expression of PFT results:*** Pulmonary function will be expressed both as measured values and as a percentage of gender-specific predicted values using the regression equations of Hankinson (29) for spirometry, Crapo (20) for subdivisions of lung volume and Neas (21) for single-breath D_LCO. For spirometry, the race-specific regression equations of Hankinson (29) will be used for African-Americans and Mexican-Americans. Adjustments of reference values for TLC, RV, RV/TLC, for African-Americans will be performed using factors recommended by the ATS (3). The race-specific equations of Neas et al. (21) will be used for calculation of the predicted values of D_LCO and D_L/V_A for African-Americans.

4.6.3.5 ***Quality Control:*** Full technical details for each test and of the quality control procedures that will be used to promote accurate and reliable measurements of spirometry, lung volumes and D_LCO are presented in the description of the Pulmonary Function Quality Control core (see PFT Manual of Procedures). Numeric and graphic pulmonary function results will be mailed to the Pulmonary Function Quality Control Core laboratory at regular intervals. Receipt of these data will be tracked with the help of the DCC. Clinical centers will receive reminder notices if these data are not received in a timely fashion.

4.6.4 Thoracic high-resolution computed tomography (HRCT). Thoracic HRCT will be performed at baseline and at 24-months using a standardized volume acquisition protocol developed by the UCLA HRCT Core. Multidetetcor CT scanners with 8 detectors will be required as a minimum; wherever possible 16 and 64 channel scanners will be used to minimize breath-hold times. Procedures will closely follow those that the UCLA-based Radiology Core has implemented successfully in other multi-center studies, including the NIH funded Feasibility of Retinoids for the Treatment of Emphysema trial (FORTE) (70)

and SLS I (85). The subject will be imaged prone and at suspended end-inspiration (TLC). Technologists will be trained to coach maximal inspiratory breath-hold from the subject and will instruct them to "Take your biggest breath in until you feel your lungs are completely full, in the same way you do in the lung function laboratory, and then signal when you feel completely full and hold your breath." Signaling will be accomplished by having subjects rotate their ankle and bring their toes together when their lungs are completely full. Technologists will again remind subjects to hold their breath for the entire scan. The breath-hold time will be 4, 6 and 10 seconds for 64, 16 and 8 detector scanners, respectively.

A clinical interpretation of each HRCT will occur at each center as part of good clinical practice and a formal radiologic report will be generated for the subject's medical record. In addition, the SLS II Radiology Core will screen the baseline HRCT for specific abnormalities that may lead to exclusion from the trial including, but are not limited: pulmonary nodules/masses, bronchiectasis, evidence of active infection, lobar or segmental collapse, and/or mediastinal/hilar mass(es) or nodes.

At baseline, one of two dedicated SLS Radiology Core Investigators will determine eligibility based on the presence of any GGO, the same entry criteria used for SLS I, which has been defined as a hazy parenchymal opacity through which normal lung markings are visible in either the presence or absence of reticular opacity or architectural distortion (except for extensive adjacent architectural distortion and honeycombing). Pure GGO, which occurs in the absence of reticular opacity or architectural distortion will be determined as a separate outcome measure and not as an entry criterion. Lung fibrosis will be defined as reticular opacification, traction bronchiectasis and bronchiolectasis with or without honeycomb change (clustered air-filled cysts with dense walls). The assessment of GGO and fibrosis will be performed using both visual reading, as in SLS I, and computer-based quantitative approaches using a computer-aided diagnostic technique developed by the UCLA Radiology Core as a result of the work performed as part of their study (Alveolitis and Fibrosis in Scleroderma Lung Disease) that was linked to the SLS I study.

The estimated radiation dose that subjects will receive as a result of the proposed CT scans is ~120 millirem, or 2.4% of the 5,000 millirem annual limit allowed radiation workers. Subjects will receive a total of two HRCT scans over the course of the entire 2-year study, for a total radiation exposure of 240 millirem.

4.6.5 Other pulmonary-related outcomes

4.6.5.1 ***Mahler modified dyspnea index:*** The self-administered computer-assisted version of Mahler's Baseline Dyspneic Index (BDI) will be completed by the subjects at the time of the baseline visit. The self-administered computer version of the Transition Dyspnea Index (TDI) will be completed by the participants every 6 months thereafter. The automated versions of these instruments have been validated (47). Standardized neutral instructions for self-completion of these questionnaires will be provided by the study coordinator, but the subject herself/himself will provide the answers independently of the study coordinators to minimize any chance of biasing the results.

4.6.5.2 ***Leicester Cough Questionnaire (Appendix B):*** This self-administered 19-item questionnaire for the quantitative assessment of symptoms of cough frequency and severity will be completed at baseline and every 3 months.

4.6.6 Health-related quality of life (HRQoL) questionnaires

4.6.6.1 ***SF-36:*** The 36 item Medical Outcomes Survey (SF-36) **(Appendix B)**, a generic HRQoL instrument that proved to be responsive to CYC therapy in SLS I, will be given

to subjects for self-administration during clinic visits at baseline and every 3 months. Several components of the SF-36 were significantly improved in response to CYC therapy in SLS I (78). In addition, the SF6D will be extracted from the SF-36 questionnaire administered at the same time points.

4.6.6.2 ***St. George's Respiratory Questionnaire (SGRQ):*** SGRQ **(Appendix B)**, a respiratory disease-specific HRQOL instrument that was originally developed for use in chronic obstructive pulmonary disease, has more recently been used in interstitial lung disease. It will be self-administered at baseline and every 3 months thereafter. This instrument, although not specifically designed for SSc, has recently been validated in SSc-ILD (8). It has been shown to be correlated inversely with FVC and directly with HRCT and exercise performance and to perform better in relation to exercise capacity and lung imaging than other non-respiratory-specific questionnaires for the evaluation of HRQoL in SSc-ILD.

4.6.6.3 ***UCLA Scleroderma Clinical Trial Consortium GIT 2.0*** **(Appendix B*).*** The UCLA SCTC GIT is a 75-item, self-reported measure assessing bowel involvement, emotional well-being, and social functioning administered at baseline, 12 months, 24 months.

4.6.6.4 ***Health assessment questionnaire modified for scleroderma (SHAQ):*** The SHAQ **(Appendix B)** will be administered at baseline and every 3 months thereafter. The SHAQ was shown to be favorably responsive to CYC therapy in SLS I (85).

4.6.6.5 ***Health Utilities (Appendix B):*** **Scleroderma Pain and Global Questionnaire** examine patient preferences to allow estimation of the usefulness of therapy from the perspective of both the patient and society. Subjects will answer five questions, each consisting of 5 Likert scales from "much better" (1) to "much worse" (5) at baseline, and every 3 months thereafter.

4.6.6.6 ***Health Care Utilization (Appendix B):*** Costs will be calculated for the outpatient, inpatient, and emergency room visits; costs associated with laboratory blood work; and costs associated with radiological testing. Indirect costs in the SLS II will be assessed using Work Productivity Survey that assesses days missed from work or worked part-time due to disease and/or treatment. This form will be administered at baseline and every 3 months thereafter.

4.6.7 Skin thickness and function scores. Skin thickness score will be quantified using the modified Rodnan measurement method, with a maximum of 51. Clinical assessment of skin thickness will be made in each of 17 body areas with 0-3 score (0 = normal; 1= mild thickness; 2 = moderate; 3 = severe thickness). Documented coefficient of variation is 12% for intra-observer reliability and 25% for inter-observer variability (17,18). Skin thickness scores were found to be significantly improved with CYC therapy in SLS I (85). A determination of "Active hand spread" of both hands will also be made. Measurements are in millimeters from the most external point of the thumb to the most external point of the most lateral finger. The average of the right and left hand spread measurements will be used (18). These measurements will be done at screening and every 3 months.

4.6.8 Musculoskeletal assessment. Creatinine phosphokinase (CPK) will be evaluated as a percent of upper limit of normal and a Joint tenderness index will be measured at screening and every 6 months. This index measures the tenderness and swelling (on a 0-3 scale) of 8 joints: bilateral elbows, wrists, metacarpophalangeal and knees, as mild, moderate or severe

(1-3) or as absent (0), for a maximum abnormal score of 24 for swelling and 24 for tenderness

4.6.9 Blood collection and skin biopsies for the Biological Specimen Repository. SLS II will serially collect and store biological specimens for ancillary studies that will address the underlying biology and mechanisms associated with SSc-ILD and its response to treatment. The ancillary studies that have been proposed to date are described in Section 1.2.4. Serum, plasma and buffy coat will be collected and prepared on-site at baseline, 12 months and 24 months. Specimens will be stored at $\leq$ -70°C and then shipped in batches to the central repository at the Rheumatology Division research laboratory at University of Texas Medical School in Houston. SLS II will take advantage of the existing NIH-funded repository that Dr. Mayes supervises and thereby register and store samples at a nominal cost. Dr. Mayes will also carry out a panel of autoantibody tests (Smith, RNP, SS-A/SS-B, Scl-70 and RNA polymerase) to further characterize the autoimmune features of our study population. Additional blood samples will be collected at baseline, 12 month and 24 month using special CPT tubes and/or PAXgene RNA collection tubes for processing. The CPT samples will be centrifuged on site and shipped by overnight courier to UCLA where they will be processed and cryopreserved as aliquots of purified peripheral blood mononuclear cells suitable for flow cytometry analysis. These samples will be stored in liquid nitrogen and then shipped in batches to the Rheumatology Division research laboratory at the University of Texas Medical School in Houston for longer-term storage. Blood samples collected in PAXgene RNA collection media will be processed on-site, stored at $\leq$ -70°C and then shipped in batches to the central repository at the Rheumatology Division research laboratory at the University of Texas Medical School in Houston. Full-thickness 4 mm punch biopsies, sliced in half, will also be obtained from the forearm skin of subjects for additional mechanistic studies at baseline and 24 months. One-half biopsy will be placed in an RNA preservative reagent. The second-half biopsy will be fixed on-site and then shipped for paraffin-embedding at a central pathology laboratory at UCLA. All samples will be forwarded to the central repository for storage. The Executive Committee will oversee all requests (both internal and external to the study) to access these samples for ancillary studies.

4.6.10 Sub-studies:

4.6.10.1 ***PROMIS-29****:* Subjects enrolling after approval of LOA #1 will complete an additional quality of life questionnaire at each 3-month visit. The PROMIS-29 assesses physical functioning, anxiety, depressive symptoms, fatigue, sleep disturbance, satisfaction with social roles, and pain. It will take about 10 minutes to complete.

4.6.10.2 ***Vitamin D Sub-Study*** Subjects enrolling after approval of LOA #1 will be given the option of having one additional blood sample (0.5 cc of serum) collected for Vitamin D and other testing. This will be drawn at the same time as other blood samples at UCLA and therefore will not require an extra needle stick

4.7 TOXICITY ASSESSMENTS

Several of the Study Outcome Assessments, as detailed in Section 4.6, will serve a dual role as toxicity assessments including the medical history and physical exam, vital signs, and the clinical reading of the thoracic HRCT. In addition, specific laboratory assessments will be carried out to assure that known clinical complications associated with scleroderma or with

either of the study drugs, CYC and MMF, will be detected and treated in a timely manner. The following routine laboratory assessments will be carried out:

4.7.1 Renal function. Renal function will be assessed by serum creatinine, glomerular filtration rate (GFR) estimated from the Modification of Diet in Renal Disease (MDRD) study equation (corrected to 1.73 square meters body surface area), spot creatinine/protein ratio (measured only when indicated for renal crisis) and urinalysis including microscopic (screen, biweekly for 2 months and monthly thereafter).

4.7.2 Complete blood count. CBC includes hemoglobin, hematocrit, white blood cell count, differential count and platelet count, as well as smear at screen, semimonthly for 2 months and monthly thereafter.

4.7.3 Multiphasic chemistries. Chemistries will include serum albumin, ALT, AST, alkaline phosphatase, bilirubin, cholesterol, creatinine, BUN/SUN, serum glucose, serum globulin, serum calcium and will be measured every 3 months for 24 months.

4.7.4 Pregnancy test. Urine pregnancy testing of female participants of child-bearing potential will be carried out at study entry and at each clinic visit while the subject is receiving study drug.

4.8 DETAILED DESCRIPTION OF STUDY VISITS

The events that will occur at each of the study visits are outlined in this section and summarized in Table 1, which can be found in the Protocol Synopsis and at the end of **Section 4** of the protocol.

4.8.1 First visit (screening visit). In order to determine eligibility, the following will take place at the first visit:

- **Complete medical history** and **physical examination** that will include assessment of dyspnea and examination of skin, chest, abdomen, legs and head (but not including a rectal or vaginal exam) to assess the extent of SSc.
- Pulmonary function tests: **spirometry** and **D_LCO.** If the subject has had spirometry and/or DLCO, performed, for clinical purposes, but otherwise meeting the quality control requirements of the study within 40 days of the baseline visit (visit 2), it/they may be submitted.
- Laboratory tests (on urine and approximately 60 cc of blood): **CBC, platelets, chem panel, CPK, urinalysis**, and **pregnancy test for women of childbearing potential.** If the subject is scheduled for HRCT the following day, the laboratories will be performed at the local laboratory on a STAT basis and also sent to the central laboratory (two samples).

Subject eligibility for participation in this study will be determined by the duration, type, and extent of disease and by the medications currently being used and used in the past, as outlined under Inclusion/Exclusion criteria.

If subjects are determined to be eligible at this point, they will then be asked to undergo a thoracic **high resolution chest CT scan (HRCT)** to assess the presence and extent of GGO and fibrosis (reflected by reticulations, traction bronchiectasis and architectural distortion with or without honeycombing) in the lungs and to exclude clinically significant pleuropulmonary disease other than SSc. To be eligible for randomization, subjects must exhibit evidence on HRCT of any GGO. If the subject has had an HRCT, performed for

clinical purposes, but otherwise meeting the quality control and scanner requirements of the study within 40 days of the baseline visit, it may be submitted for the reading.

4.8.2 Second visit (baseline visit). Subjects will return to their study physician within 40 days of their initial evaluation to discuss the results of the testing. If they have not met study enrollment criteria, then their participation will end. If they meet all study inclusion and exclusion criteria up to this point, the following studies will take place:

- Pulmonary function test: **spirometry and lung volumes.** If the subject has had lung volumes performed, for clinical purposes, but otherwise meeting the quality control requirements of the study within 40 days of the baseline visit (visit 2), they may be submitted. The spirometry must be completed on a separate day from the visit 1 (screening) spirometry.
- If the %-predicted FVC is within 10% points of the value obtained at screening and is > 45% and ≤ 85% predicted, the subject will continue with the visit. If the repeatability or lower limit criteria are not met, testing will end for the day and a repeat FVC measurement may be obtained within 7 days, at the discretion of the subject, to determine if it meets entry criteria. The two spirometries with the highest repeatable FVC will be used as screening and baseline in the order they were performed.
- If the repeat %-predicted FVC fails to be within 10% of the value obtained at screening or is not > 45% and ≤ 85% predicted, the subject's participation in the study will terminate.
- If the subject meets the repeat FVC inclusion criteria at the second visit or on repeat testing within 7 days, they will proceed with the remainder of testing.
- One optional full-thickness 4 mm **punch biopsy** will be obtained from the forearm skin if they have specifically consented to do so.
- Questionnaires: **Self-Administered version Mahler's Baseline Dyspnea Index (BDI), SHAQ**, **SF-36** (and associated **SF-6D**), **SRGQ**, **Scleroderma Pain and Global Questionnaire**, **Leicester Cough Questionnaire, UCLA SCTC GIT 2.0, Health Care Utilization and PROMIS-29.**
- **Blood collection for repository** (approximately 40 cc).
- **Pregnancy test for women of childbearing potential.**
- Upon completion of successful repeat FVC testing, the site coordinator will complete the online study enrollment form and randomization will occur. The site coordinator will contact the UCLA PTL to confirm subject randomization and the subject will be assigned to receive a study drug 2 week starter kit according to the predetermined randomization schedule for the site. Randomization will occur in a double-blinded manner and neither the physician nor the subject will know their treatment assignment.

4.8.3 Interim visits (0-24 months). There are a number of potential side effects of the study drugs that can be detected only through regular blood and urine testing. Subjects will be required to attend a clinic every two weeks for the first two months and every month thereafter for blood (1 ½ - 3 ½ teaspoons) and urine tests: CBC, platelets, urinalysis, and pregnancy test for women of childbearing potential. Based on their tolerance of the medication and the results of this laboratory testing, their dosage of medication will be adjusted which would require additional interim visits every 2 weeks until the proper dose is achieved.

4.8.4 Three-month visits. They will return to the study physician after they have been on the study medication for 3 months (and every 3 months thereafter for a total duration of 2 years) and the following will take place:

- Detailed examination of the extent and severity of their scleroderma including **history** and **physical examination**
- Pulmonary function tests: **spirometry and D_LCO**
- At every other three-month visit (i.e., every 6 months) **lung volumes** will also be performed.
- Questionnaires: **SHAQ**, **SF-36** (and associated **SF-6D**), **SRGQ**, **Scleroderma Pain and Global Questionnaire**, **Mahler's Dyspnea Index (the TDI will be performed every 6 months), Leicester Cough Questionnaire, Health Care Utilization and PROMIS-29.**
- Laboratory tests (on urine and approximately 60 cc of blood): **CBC, platelets, chem panel, CPK, urinalysis, pregnancy test for women of childbearing potential and Vitamin D (if provided consent for sub-study).**

4.8.5 One year (12 month) visit. In addition to the standard 3 month testing, **blood collection for the repository** (approximately 40 cc) and the **UCLA SCTC GIT 2.0** Questionnaire will also take place at the one year visit.

4.8.6 Two-year visit (end of study). Subjects will return to the study center after two years in the study at which time the following will take place:

- Detailed examination of the extent and severity of their scleroderma including a **complete history** and **physical examination**
- Pulmonary function tests: **spirometry, D_LCO and lung volumes**
- One optional full-thickness 4 mm **punch biopsy** will be obtained from the forearm skin if they have specifically consented to do so.
- Questionnaires: **SHAQ**, **SF-36** (and associated **SF-6D**), **SRGQ**, **Scleroderma Pain and Global Questionnaire, Mahler's Dyspnea Index, Leicester Cough Questionnaire, UCLA SCTC GIT 2.0, Health Care Utilization and PROMIS-29.**
- Laboratory tests (on urine and approximately 60 cc of blood): **CBC, platelets, chem panel, CPK, urinalysis, pregnancy test for women of childbearing potential.**
- **Blood collection for the repository** (approximately 40 cc)

4.8.7 Long-term follow-up. Subjects will be consented for, and contact/tracking information collected for, long-term follow-up of up to 12 years. Presently they will be followed until the end of the study. If funding is available, the National Death Index, cancer registries and similar databases or medical records will be queried for long-term complications of the immunosuppressive medications such as cancer, latent virus infections, reproductive difficulties and cardiovascular complications, and SSC, for up to 12 years following enrollment.

4.8.8 Schedule adjustment for subjects impacted by drug shortage. In the summer of 2011, it became apparent that there would likely be a brief interruption in supplying a minority of subjects with study drug due to a manufacturer shortage. These subjects may not be resupplied with study drug as planned and may therefore go off of study drug for a short time; both CYC and MMF may be stopped to maintain the blind. Study visits will continue during any study drug interruption. In order to ensure 24 months of treatment for all subjects,

subjects who are off blinded study drug for more than two weeks will have their study participation and study drug extended for the same length of time that they are off study drug. For these subjects, the two-year visit described above will occur at the end of this extended period, and an interim visit will occur in place of the regularly scheduled 2-year visit. For example, if a subject is off study drug for 1 month due to this shortage, he/she would have an interim visit at 24 months, remain on study drug for 1 additional month, and have an end of study visit at 25 months when he/she completes his/her treatment. Please note that subjects who are off study drug for 2 weeks or less will not undergo a schedule adjustment and will complete visits as described above.

4.9 DEFINITION AND HANDLING OF TREATMENT FAILURES

Subjects who, after > 3 months of study, demonstrate a fall in percent-predicted FVC ≥ 15 percentage points from their baseline determination will be classified as "treatment failures" (i.e., an initial FVC of 75%-predicted would need to drop to ≤ 60%-predicted to be classified as a treatment failure). A treatment failure will also be defined when the FVC falls below a lower limit of < 35%-predicted, regardless of the absolute change from baseline (e.g., an initial FVC between 45% and 49% that declines to ≤ 35%). To meet these definitions, subjects must have two FVC measurements greater than 15 days apart, both showing a decrement of ≥ 15 percentage points from baseline and/or a FVC %-predicted of ≤ 35%. Subjects with treatment failures will be withdrawn from the double-blind portion of the trial. The clinical management of treatment failures will be at the discretion of the patient and their treating physician. The study blind will not be broken unless the treating physician is convinced that unblinding is required in order to appropriately treat the patient. Subjects who fail treatment will be encouraged to return to the clinic every 6 months (i.e. for the 6-month, 1-year, 18-month, and 2-year assessments), at which time the medication prescribed by their treating physician will be recorded.

4.10 HANDLING PREMATURE PARTICIPANT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason. The investigator also has the right to withdraw subjects from the study in the event of intercurrent illness that interferes with the study, adverse events, treatment failure, significant protocol violations or for other reasons as defined by the protocol. Should a participant prematurely withdraw or be withdrawn from the study for any reason he/she will be asked to return for study visits every 6 months (i.e., at 6 months, for the One-Year Visit, at 18 months, and for the Final Visit (at 2 years) as outlined above). The participant will also be asked to participate in an exit visit, either by phone or in person, to document the reason for withdrawal and the status of the participant at the time of the withdrawal. Should the participant die, the cause of death will be determined and recorded if possible. This additional data will be utilized in the statistical analysis of the primary and secondary study outcomes and any missing data handled by appropriate statistical methods.

4.11 SUMMARY OF PROTOCOL VISITS AND ASSESSMENTS

Table 1. Schedule of Assessments

	Months after randomization																											
	Scn	BL	0.5 ±4d	1± 4d	1.5± 4d	2± 7d	3± 10d	4± 7d	5± 7d	6± 10d	7± 7d	8± 7d	9± 10d	10± 7d	11± 7d	12± 10d	13± 7d	14± 7d	15± 10d	16± 7d	17± 7d	18± 10d	19± 7d	20± 7d	21± 10d	22± 7d	23± 7d	24± 10d
General H&P	X																											X
SSc-H&P, vitals	X						X			X			X			X			X			X			X			X
Rodnan skin score	X						X			X			X			X			X			X			X			X
Lung exam	X						X			X			X			X			X			X			X			X
Mahler Dyspnea		X								X						X						X						X
SHAQ, SF-36, SGRQ, Leicester Cough Questionnaire, SSc pain/global , Health Care Utilization & PROMIS-29		X					X			X			X			X			X			X			X			X
UCLA SCTC GIT		X														X												X
LABS:																												
CBC, plat	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chem panel	X						X			X			X			X			X			X			X			X
CPK	X						X			X			X			X			X			X			X			X
Urinalysis	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preg test +	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRCT	X*																											X
Toxicity monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PFTs:																												
Spirometry	X	X**					X			X			X			X			X			X			X			X
DLCO	X						X			X			X			X			X			X			X			X
Lung volumes		X								X						X						X						X
Blood for repository		X														X												X
Skin biopsy for repository***		X																										X
Vitamin D***							X			X			X						X			X			X			

*To take place within 40 days of Screening Visit if meet all other inclusion criteria

** Screen and Baseline FVC must be within 10% - repeat within 7 days if not

*** Optional – not required to undergo skin biopsy and Vitamin D Sub-study in order to participate in study

+ For women of childbearing potential

5. SAFETY MANAGEMENT

5.1 CLINICAL INVESTIGATOR SAFETY RESPONSIBILITY

The Clinical Investigator (site physician involved in patient care) will be a key figure in safety monitoring. The Clinical Investigator, who is also blinded to treatment assignment, will assess patient health over the course of the study, including tracking of overall health and medication use, review all toxicity laboratories and assessments (within 3 days of testing), review all adverse events and serious adverse events, and initiation of requests for study drug dose adjustments and/or additional monitoring according to the study protocol and good clinical practice. Any time a clinically important treatment-related adverse event occurs, the Clinical Investigator will contact the DCC, site study coordinator, and the Pharmacy Core and prescribe a change in medication and/or additional testing monitoring according to the predetermined study protocol (see section 5.7). If a subject is hospitalized either at the participating center or elsewhere, this information will be transmitted to the Clinical Investigator and the site PI (if not the Clinical Investigator). Serious adverse events (SAEs), including hospitalizations, or the occurrence of grade IV or V toxicity will necessitate communication with the DCC within 24 hours. How medication should be changed will be determined by the Clinical Investigator locally, using the protocol that has been developed to provide a nearly uniform response to toxicity at all centers. The same safety information will be transmitted to the Data Safety Monitoring Board (DSMB). Timely communications regarding grade IV and V toxicity and SAEs will be made so that appropriate and timely decisions can be made about continuing the trial *in toto* as well as making appropriate medication changes in the subject.

While the Clinical Investigator might be unmasked by the nature of some toxicity results, such as hematuria (which is expected to occur in both treatment arms but at a higher frequency in the CYC arm), or when a subject's study assignment is purposely unmasked according to specific protocol criteria, CYC and MMF otherwise share a similar toxicity profile that will limit unintended unmasking.

5.2 RISKS ASSOCIATED WITH USE OF CYC

5.2.1 **Allergic:** Rare anaphylactic reactions have been reported; including cases associated with death.

5.2.2 **Carcinogenesis:** Second malignancies, sometimes delayed several years, may occur with CYC alone and most frequently involve the urinary bladder, myeloproliferative, or lymphoproliferative malignancies. Lifetime risk is not clearly defined with chronic oral use but probably < 5% after 1 year CYC exposure.

5.2.3 **Digestive System:** Nausea and vomiting commonly occur with CYC therapy (up to 30-40%). Anorexia and, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy. These adverse drug effects generally remit when cyclophosphamide treatment is stopped.

5.2.4 **Fertility and Reproductive Track:** CYC interferes with oogenesis and spermatogenesis in a dose- and duration-dependent manner and may cause sterility in both sexes. CYC-induced sterility may be irreversible in some patients.

Amenorrhea (up to 50%) and oligospermia or azoospermia may also occur (up to 100%). Sexual potency and libido are not affected.

5.2.5 **Fluid and Electrolytes:** SIADH (syndrome of inappropriate ADH secretion) has been reported with the use of CYC.

5.2.6 **Hematologic:** CYC suppresses hematopoietic function in a dose- and duration-dependent manner resulting in leukopenia, thrombocytopenia and anemia (up to 30-40%).

5.2.7 **Infections:** Immune suppression that can increase susceptibility to and severity of infections including those of viral, bacterial, fungal, protozoan, or helminthic origin (up to 30%).

5.2.8 **Lactation and Nursing:** CYC is excreted in breast milk and due to its potential for serious adverse reactions and tumorigenicity its use is contraindicated during breastfeeding.

5.2.9 **Pregnancy:** Rated category "D". CYC can cause fetal harm when administered to a pregnant woman although normal infants have also been born to women treated with CYC during pregnancy.

5.2.10 **Skin and Hair:** Skin rash occurs rarely (<2%) but alopecia occurs commonly (up to 50-60%).

5.2.11 **Urinary System:** Dose- and duration-dependent changes to the urinary system may occur due to metabolites excreted in the urine and include hemorrhagic cystitis (up to 20%), which can be severe and even fatal in rare cases, fibrosis of the urinary bladder, sometimes extensive, and atypical urinary bladder epithelial cells in the urine.

5.2.12 **Wound Healing:** CYC has been reported to interfere with wound healing.

5.3 RISKS ASSOCIATED WITH USE OF MMF

5.3.1 **Allergic:** Rare allergic reactions to MMF have been observed.

5.3.2 **Carcinogenesis:** Patients receiving immunosuppressive regimens involving combinations of drugs, including MMF, are at increased risk of developing lymphomas and other malignancies, particularly of the skin, in a dose- and duration-dependent manner. Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving MMF (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of organ transplants.

5.3.3 **Digestive System:** Nausea, abdominal pain, constipation and diarrhea are reported in patients taking MMF. GI bleeding (requiring hospitalization) has been observed in up to 5% of transplant recipients treated with MMF 3 g daily. Gastrointestinal perforations have rarely been observed. MMF is associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation.

5.3.4 **Hematologic:** Severe neutropenia [absolute neutrophil count (ANC <500) developed in up to 4% of transplant recipients receiving MMF 3 g daily and may

be related to MMF itself, concomitant medications, viral infections, or some combination of these causes. Anemia and thrombocytopenia have also been reported. Pure red cell aplasia (PRCA) has been reported in patients treated with MMF in combination with other immunosuppressants. Dose reduction or elimination appears to improve PRCA.

5.3.5 **Infections:** Immune suppression that can increase susceptibility to and severity of infections, including fatal infections.

5.3.6 **Lactation and Nursing:** MMF is excreted in breast milk in animal models and due to its potential for serious adverse reactions and tumorigenicity its use is contraindicated during breastfeeding.

5.3.7 **Pregnancy:** Pregnancy Category "D". MMF can cause fetal harm when administered to a pregnant woman. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss (30-45%) and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney (18-22%). MMF is also known to alter the effectiveness of hormonal-based contraceptives.

5.3.8 **Latent polyomavirus reactivation:**

Progressive Multifocal Leukoencephalopathy (PML)/JC virus reactivation: Cases of progressive multifocal leukoencephalopathy, sometimes fatal, have been reported in patients treated with MMF. The reported cases generally had additional risk factors for progressive multifocal leukoencephalopathy, including treatment with multiple immunosuppressant therapies and impairment of immune function.

BK Virus associated nephropathy/BK virus reactivation is associated with renal allograft dysfunction. This has been reported with the combination of MMF and tacrolamus, but has also occurred with cyclosporine, azathioprine and sirolamus. BK nephropathy rarely occurs in the native kidneys in non-renal solid organ transplant recipients. In hematopoietic (usually allogenic) cell transplantation recipients, episodes of urinary BK viral shedding may precede hemorrhagic cystitis.

Three additional viruses are in this family, but have not been associated directly with MMF: **KI and WU viruses** have been associated with respiratory illness and **Merkel cell virus** (MC virus) may be causative of Merkel cell carcinomas of the skin. These must be considered hypothetical risks of immunosuppression.

5.3.9 **Skin:** Skin rash has been reported in patients taking MMF.

5.4 APPROACHES FOR MINIMIZING RISKS

Due to the frequent and sometimes serious risks associated with the two study drugs, specific measures have been instituted to minimize these risks and improve the risk:benefit ratio for participants. First, based on past experience with the administration of CYC to patients with SSc-ILD, the inclusion and exclusion criteria have been selected to enrich for subjects most-likely to benefit from therapy (see Inclusion Criteria) and to avoid those subjects who are less-likely to

benefit or more likely to experience treatment-related toxicity (see Exclusion Criteria). Concurrent medications that adversely interact with the study drugs or with the potential adverse effects of the study drugs will be excluded. Pregnancy status will be carefully evaluated, institution of appropriate precautions verified in participants of childbearing potential, and pregnancy status monitored throughout the study. In addition, frequent and routine laboratory monitoring will be carried out throughout the entire study protocol. Clinical Investigator is responsible for reviewing and acting on toxicity data in accordance with a protocol-defined action plan. The Clinical Investigator will be guided in the management of study drugs by detailed protocols for modifying drug dosing in the event of specific adverse events. In view of a recent FDA warning concerning the occurrence of progressive multifocal leukoencehalopathy in subjects receiving MMF (always in conjunction with other immunosuppressive therapy), subjects in SLS II will be monitored closely for evidence of any neurologic symptoms or findings suggestive of the early development of progressive multifocal leukoencephalopathy, such as apathy, confusion, cognitive deficiencies, ataxia or hemiparesis.

5.5 ADVERSE EVENT REPORTING

An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). All AEs must be recorded even if a causal relationship to the study drug is unlikely.

Patients are instructed to report any AE to the investigator. On each day of evaluation, the patient is questioned in a general way regarding any new medical problems and new or changed medications. All AEs are documented in the source document and on appropriate AE case report forms. The intensity of all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE; view online at http://ctep.cancer.gov/reporting/ctc_v30.html) using the following scale:

- Grade 0 = No AE = within normal limits
- Grade 1 = Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)
- Grade 2 = Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery])
- Grade 3 = Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)
- Grade 4 = Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation)
- Grade 5 = Fatal AE

5.5.1 The relationship of an AE to study treatment will be characterized as “probably related”, “possibly related”, or “unlikely related” by the study center physician according to the following guidelines:

5.5.1.1 ***Probably Related.*** This category applies to those adverse events that are considered with a high degree of certainty to be related to the test drug. Attributes of such a relationship may include some or all of the following:

- It follows a reasonable temporal sequence related to drug administration
- It cannot be reasonably explained by other known characteristics of the participant
- It improves/resolves upon stopping study drug
- It occurs in a pattern/manner known or suspected to be related to study drug
- It reappears upon rechallenge with study drug

5.5.1.2 ***Possibly Related.*** This category applies to those adverse events for which a cause and effect relationship between the study drug and the AE has not been previously demonstrated and it appears unlikely from the known effects of the drug, but cannot be ruled out with certainty. Attributes of such a relationship may include some or all of the following:

- It follows a reasonable temporal sequence related to drug administration
- It may be reasonably explained by other known characteristics of the participant or their treatment for other conditions, but cannot determine the cause with any degree of certainty
- It occurs in a pattern/manner known or suspected to be related to study drug

5.5.1.3 ***Unlikely Related.*** In general, this category is applicable to adverse events that meet some or all of the following criteria:

- It does not follow a reasonable temporal sequence related to drug administration
- It likely to be explained by other known characteristics of the participant or their treatment for other conditions
- It does not follow a pattern/manner known or suspected to be related to study drug
- It does not resolve when the drug is stopped or reappear/worsen when the drug is re-administered.

5.6 SERIOUS ADVERSE EVENT REPORTING

A serious adverse event (SAE) is defined as one that meets the criteria below. The Investigator must report any SAE to his/her IRB within 48 hours, to the UCLA DCC and to the FDA as described in *21 CFR §312.32 (IND Safety Reports)*. The criteria for defining an SAE include:

- An event that is fatal, resulting in death
- An event that is life threatening. In the opinion of the study center physician, the patient was at immediate risk of death due to the event as it occurred;
- An event that results in persistent or significant disability/incapacity;
- An event that results in a congenital anomaly/birth defect;
- An event that requires inpatient hospitalization or prolongs hospitalization;
- An important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

5.7 DOSE MODIFICATIONS FOR TOXICITY

The toxicity profiles for CYC and MMF are well established as outlined in Section 5.7.2 and drug discontinuation and/or dose modification will be managed by the Clinical Investigator (see section 5.7.3) using the following specific criteria:

5.7.1 Reasons for withholding the dose of study drug: The following abnormalities and laboratory tests require study drug discontinuation, either temporary (until normalization) or permanent, as indicated by the nature of the event, its severity and/or course of resolution upon discontinuation of therapy.

- Allergic reaction associated with drug administration
- WBC <2500, or < 1000 neutrophils
- Platelet count < 100,000
- Hemoglobin < 10.0 gm/dl or a drop in hemoglobin to < 9.0 gm/dl if the baseline hemoglobin was < 11.0 gm/dl
- Documentation of gastrointestinal ulcer, bleeding or abdominal emergency
- Pregnancy or initiation of breastfeeding
- Intractable congestive heart failure
- Serum creatinine > 2.0 mg/dl, or increase in serum creatinine of > 50% over baseline, or decrease of estimated GFR to < 45 ml/min/1.73 m^2 (corrected) in the absence of other etiology
- Hematuria with > 50 RBCs/hpf, in the absence of other etiologies (i.e., urinary tract infection, renal stone, menses)
- Ongoing infection whose management would be significantly compromised by continued drug-associated immunosuppression
- Development of a proven malignancy other than basal cell cancer of the skin or cervical carcinoma in situ removed entirely by biopsy
- Any adverse event felt by the investigator to be possibly or probably related to a study drug and of a clinical significant sufficient to warrant drug discontinuation

5.7.2 Management of drug dosing in response to specified toxicities. If any of the above toxicity occurs, the dose of study medication will be altered as follows:

5.7.2.1 Allergic reaction; pregnancy or breastfeeding; proven malignancy: Study drug will be stopped and subject withdrawn from study.

5.7.2.2 Bone Marrow Suppression: For leukopenia (WBC < 2500 and/or ANC < 1000), thrombocytopenia (< 100,000), or anemia (Hgb < 10 gm/dl) the study drug will be managed as follows:

- Hold study drug until there is a stabilization of the hematologic abnormality at a value above the toxicity threshold levels (either 9.0 gm/dl or 10.0 gm/dl, depending upon the individual subject's baseline WBC > 2500, platelets > 100,000). In addition, if another cause for the reduction in hemoglobin is found (e.g., gastrointestinal bleeding), that cause should be appropriately

treated and determined by the study physician to be stable before restarting on study drug.

- Once threshold values are exceeded, the study drugs (MMF or CYC/Placebo) will be reintroduced at by starting over with the patient's weight-adjusted dose titration and the dose advanced every 2 weeks as tolerated. At the site investigator's discretion, after taking into account whether the study drug was likely or probably related to the adverse event, the final maintenance dose may be either the last regular dose taken by the patient or one capsule per-dose less (500 mg/day less for MMF or 25 mg/day less for CYC). The final target dose must be specified by the site investigator at least two weeks in advance and communicated to the DCC and the Pharmacy Core using the Toxicity Management Form.
- Follow-up should be every 1-2 weeks, as clinically indicated, until the investigator is satisfied that it is safe to return to the protocol-defined dosing schedule.
- In the event of repeat toxicity, the same cycle should be repeated except with the intention of achieving a maintenance dose equal to 2 capsules per dose less than the highest dose previously taken (1000 mg/day less for MMF or 50 mg/day less for CYC).

5.7.2.3 Hematuria: Drug management in response to hematuria will be adjusted as outlined in **Table 6** (if menstruating, re-check urinalysis 1 week later before proceeding):

Table 6. Management of Hematuria

Urinalysis		Management
0-10 RBC/HPF	→	Continue study drug and routine monitoring
10-25 RBC/HPF	→	Repeat urinalysis in 1 week
> 25 RBC/HPF or 10-25 RBC/HPF on 2 occasions	→	Hold study drug, collect urine C&S, check platelet count and PT/PTT, and manage according to the following rules: • If urine C&S, platelet count and PT/PTT are unrevealing, perform cystoscopy. • If urine C&S positive, treat with antibiotic and resume study drug at same dose. • If platelet count decreased, see cell count toxicity protocol. • If PT/PTT prolonged, evaluate etiology and resume study drug. • If the subject is on anticoagulation, hold study drug and perform cystoscopy. o If cystoscopy is without evidence of hemorrhagic cystitis or malignancy, then resume drug study. Evaluate other etiologies of hematuria. o If cystoscopy reveals hemorrhagic cystitis or malignancy, then subject exits study.

5.7.2.4 For hospitalizations, surgery or infections requiring antibiotics where the immunsuppressive effects of the study drugs are determined by the investigator to likely complicate the clinical course: The study drug should be discontinued until the potential interaction with the medical condition in question has resolved. Once the patient is stable, the study drug can be restarted without dose modification.

5.7.2.5 Other severe or dangerous adverse events: For adverse events that are considered clinically serious by the investigator, the study drug will be managed as follows:

- Hold study drug until there is resolution of the adverse event.
- Once stable, the study drugs (MMF or CYC/Placebo) will be reintroduced by starting over with the patient's weight-adjusted dose titration and the dose advanced every 2 weeks as tolerated. At the site investigator's discretion, after taking into account whether the study drug was likely or probably related to the adverse event, the final maintenance dose may be either the last regular dose taken by the patient or one capsule per-dose less (500 mg/day less for MMF or 25 mg/day less for CYC). The final target dose must be specified by the site investigator at least two weeks in advance and communicated to the DCC and the Pharmacy Core using the Toxicity Management Form.
- Follow-up should be every 1-2 weeks, as clinically indicated, until the investigator is satisfied that it is safe to return to the protocol-defined dosing schedule.
- In the event of repeat toxicity, the same cycle should be repeated except with the intention of achieving a maintenance dose equal to 2 capsules per dose less than the highest dose previously taken (1000 mg/day less for MMF or 50 mg/day less for CYC).

5.7.2.6 For less severe or dangerous adverse events (e.g., dyspepsia) not responding to concomitant medications: the study drugs are to be discontinued until the adverse event disappears, at the clinical discretion of the study physician. At that point the subject can be restarted at one-half of the original dose. The subject can return to the full dose of medications or one capsule less than the full dose, as clinically indicated, after 2 weeks at the half dose of medications. All voluntary plans for adjusting study drug dosing must be approved in advance by the DCC and the pharmacy, and subsequently documented on a Toxicity Management Form, so that appropriate replacement drug can be provided.

5.7.3 Discontinuation of study drug for unresolved toxicity: If the subject cannot resume study medication at some dose within one month of discontinuing, secondary to adverse or other events: the subject should be discontinued from the trial and the subject should complete the one- and two-year visits.

5.8 DATA AND SAFETY MONITORING BOARD (DSMB)

A DSMB will be appointed by the NHLBI to provide external oversight concerning the safety and scientific integrity of the study for the duration of the clinical trial. The DSMB will review the protocol and suggest any changes that might be required prior to study implementation. Once the trial is initiated, the DSMB will review cumulative trial results to evaluate the treatment for beneficial and adverse effects. Its membership will consist of external experts (two pulmonologists, two rheumatologists, one statistician and an ethicist) who will convene every 6 months over the duration of the trial to review the progress of the study toward meeting enrollment goals, adverse and serious adverse event profiles, and study outcome measures. The DSMB, in consultation with the study sponsor (the NHLBI) and participating sites may determine at any time that the study should be modified or terminated due to toxicity

and/or futility considerations. The DCC will provide the DSMB with all of the study related information that it requires to carry out its directive. The ruling of the DSMB to modify or close the study, once all discussion and appeals have been considered, will be final.

5.9 MORBIDITY AND MORTALITY REVIEW COMMITTEE (MMRC)

A Morbidity and Mortality Review Committee consisting of three external experts (one in pulmonary medicine, one in rheumatology and one in general internal medicine) will be appointed by the DCC with the advice of the Steering Committee. The purpose of this committee will be to review all death, hospitalization records and records from unscheduled outpatient or Emergency Department visits to determine cause of death and any serious potential complications of treatment or of progression of the underlying disease. The DCC will mail death, hospital and outpatient records in accumulated batches of 12-20 records to all three members of the MMRC for their review. The MMRC will report its findings to the DCC as to the primary and secondary causes of death and the primary and secondary conditions that led to hospitalization that will be included in the analysis of mortality and morbidity data, the results of which will be reported to the DSMB. Adjudication will be required in cases in which all three members if the MMRC do not agree on the primary cause of death or two out of three on secondary causes.

6. DATA COLLECTION AND QUALITY ASSURANCE

The DCC will prepare a complete set of Case Report Forms (CRFs) to be completed by the study investigators at each clinical site and the collected information then entered into a secure web-based data reporting system linked to the Data Coordinating Center database. Forms will cover the following data collection issues and be supplemented by source documentation that will be maintained in a secure and confidential manner at each clinical site following all IRB and HIPPA guidelines.

6.1 PRE-RANDOMIZATION CRFs

Pre-randomization CRFs will document background information and the subject's disease history that are necessary for verifying the subject's eligibility for the trial, and for the future evaluation of the relationship between potential prognostic factors and results of the trial. Forms for this purpose will include:

1. Preliminary Eligibility Checklist
2. Final Eligibility Checklist
3. Medical History
4. Active Medication List
5. SSc Specific History & Physical Examination
6. Rodnan Skin Score
7. Laboratory Report
8. Screening Pulmonary Function Worksheet
9. Imaging Data Notification Form
10. CT Imaging Report
11. Radiology Referral Form
12. Core Radiologist Review Data Transfer Form
13. HRCT Site Report Form

The Preliminary Eligibility Checklist and Final Eligibility Checklist must be entered into the web database, and HRCT scans and PFT reports must be submitted to the Radiology Core and PFT Core, respectively, for review before randomization. Randomization will then be done by the DCC after Final Eligibility is approved. All other pre-study and baseline data will need to be entered by the study coordinator prior to randomization. It is the responsibility of the site study coordinator to complete the necessary forms, obtain supporting documents and submit to the cores in a timely manner.

6.2 FOLLOW-UP CRFs

The baseline and follow up forms are necessary for recording the treatments received by the subjects, for monitoring the toxicity associated with these treatments, and for monitoring the course of the disease. The forms that will be prepared for this purpose will include:

1. 3-9-15-21 Month Follow up Form
2. 6-12-18-24 Follow up Form
3. SSc Specific History & Physical Examination Final
4. Active Medication List
5. Rodnan Skin Score
6. Mahler's Baseline and Transition Dyspnea Index Grading (BDI/TDI)
7. Leicester Cough Questionnaire
8. Scleroderma Health Assessment Questionnaire (SHAQ)
9. MOS-36Short Health Survey Form (SF-36)
10. St. George Respiratory Questionnaire (SGRQ)
11. Scleroderma Pain and Global Questionnaire
12. UCSD Health Care Utilization Questionnaire
13. UCLA SCTC GIT 2.0
14. Pulmonary Function Worksheet
15. Laboratory Report
16. Drug Administration and Reconciliation Form
17. Unscheduled Visits Form
18. Safety Management Form
19. Safety Monitoring Form
20. Missed Visit Form
21. Imaging Data Notification Form
22. Radiology Referral Form
23. CT Imaging Report Form
24. Core Radiologist Review Data Transfer Form
25. HRCT Site Report Form
26. Adverse Event Report
27. Serious Adverse Event Report
28. SAE Supplemental Report
29. Study Completion/Termination Form
30. Permanent Discontinuation of Study Drug
31. In Case of Death
32. Bio-Repository Skin Sample Preparation Form
33. Bio-Respository Blood Sample Preparation Form
34. Pulmonary Function In case of Treatment Failure

The Follow-up Report Forms will be entered within 7 days (optimally within 48 hrs) after each time the subject visits the center for a scheduled treatment or will be considered delinquent if submitted after that interval. The subject will undergo physical examinations, questionnaires and laboratory tests as dictated by the protocol and the results will be recorded on the Follow-up Report Forms.

Serious toxicity and adverse event reporting will follow the guidelines set forth in the study protocol. If the subject misses a follow-up visit, the clinic research nurse will try to reschedule the appointment as soon as possible. The window time is 4 days for the 2-week visits, 7 days for the one-month visits and 10 days for the 3-month visits. If the subject is unable to visit the clinic but can be seen by his primary physician for a check-up, the principal investigator may contact the subject's physician to assess disease status. The subject's disease status and any other available follow-up information will be recorded on the Follow-up Form with a note indicating that the subject's follow-up information was obtained from the primary physician. A similar procedure will be followed if the subject moves a significant distance from the clinic. In the latter event, the principal investigator should contact the subject's new physician, explain the subject's involvement in the trial, and ask for his assistance in obtaining follow-up information. In the event that a subject completely misses a follow-up visit, the clinic research nurse will send the follow-up form to the DCC indicating on the form that the visit was missed, and include a brief explanation of why the visit was missed. This will allow the DCC to maintain an accurate account of the forms received and outstanding.

The Safety Management Form will contain the subject's medication dose and intake history.

The Study Completion/Termination Form will be completed in the event that the subject (1) expires, (2) becomes lost to follow-up and no more information can be obtained about the subject (clinic research nurse will use all available means to determine the subject's disease and vital status), (3) completes the study treatment, (4) Study failure.

6.3 DATA RECORDING, ENTRY, TRANSMISSION AND STORAGE

6.3.1 Data collection and recording on CRFs. Subject-specific clinical information will be abstracted from patient charts, PFT reports, radiological exam reports, and laboratory forms and entered onto paper CRFs. The Study Coordinator will review forms for errors and make sure each form is complete before logging onto the secure web database entry system. A complete record of the source documents and CRFs will be maintained on site and be available for validation of collected study information.

6.3.2 Web-based data entry and transmission. Web design and programming of the data entry system will be prepared by Semel Institute Statistics Core (SIStat). The programmer at SIStat will create a user-friendly web-based data entry system that has the following characteristics:

1. The visual screen formats on the computer will be similar to the actual forms.
2. Fields will have range boundaries (where appropriate) that will be checked automatically as the data are entered.
3. Default values will be incorporated into the data entry system to minimize typing and maximize efficiency.
4. Objects such as drop down lists, check boxes and toggle buttons will be used to minimize errors.
5. An automated skip pattern will be programmed so that items which are not applicable will be automatically skipped in order to reduce errors.

6. Logic checks will be used to maintain a clean database.
7. Calculations will be carried out by computer rather than by hand, reducing errors.
8. Automated email notifications with receipt and read verifications will be employed to communicate essential study notifications related to eligibility, toxicity, and dose modifications.

6.3.3 Data storage. Data will be stored on a secure file server meeting all federal regulatory guidelines for security and confidentiality. In addition, all data stored on the server is "mirrored," meaning that data is written to two hard disks simultaneously. This provides protection against a single failed hard disk drive. As added security against losing data, all files on the server are backed up each night. The responsible programmer will make additional tape backup copies of the database periodically. In addition to a Firewall to protect unauthorized access to the server, SSL Data Encryption to protect data transmission from client machine to server. The Secure Sockets Layer (SSL) technology provides protection from the login screen until users sign out. All data will be encrypted during data transmission.

User Access Control: Only authorized users are allowed to log in the system and to access authorized tasks only. System administrators have full control to manage user access. System Logs: The system keeps log on user activities, data export, data change history.

6.3.4 Data Confidentiality. All data including patient information will be carefully handled and securely stored. Patient information is stored in a locked file cabinet and only authorized personnel have the key to it.
The web server is located in UCLA Medical center server control room with security monitoring and keypad to ensure the security. Only authorized personnel can access to the server room. All computers used in the entry and storage of data will be certified by the participating institutions to comply with all federal standards for security, confidentiality and the protection of protected health information.

6.4 ROUTINE DATA REPORTING BY THE DCC

The data manager at the DCC will provide the following reports and listings to the study's Steering Committee, which includes all the PI's. All reports will be generated through the computer system.

6.4.1 Monthly Patient Accrual Report. The monthly patient accrual report, called the 'Monthly Report', will include the total number of subjects randomized to date, number of subjects in each study group, total number of subjects on-study, total number of subjects off study. Overall totals and totals by institution will be reported. The DCC coordinator will update this report during the first week of each month and will distribute it to members of the Steering Committee, Data and Safety Monitoring Board (DSMB) and the NHLBI Program Officer.

6.4.2 Progress Report. An annual progress report will be submitted to the Steering Committee, DSMB and NHLBI Program Officer describing the progress of the project during the previous 1 year and the cumulative progress of the study. The progress report will include a tabular accrual display similar to the monthly report, as well as selected analyses for various study parameters as specified in the statistical analysis section of the protocol.

6.4.3 Clinic Performance Report. The performance of each clinic will be reported quarterly to the clinical centers. The Performance Report will include, for each clinic, accrual rate, subject drop out rate, problem form, time to respond to the correction request, overdue form rate and protocol violations.

6.4.4 Forms/Materials Over Due List. During the first week of each month, the DCC coordinator will generate lists of the forms and materials due for each institution. Any form not received by one month after the target follow-up date is overdue. These lists will be accompanied by a monthly subject accrual report that will keep the participating institutions informed about the study's accrual. The subject accrual report will also be used by the data manager to pass along new information about the trial to the clinic principal investigators and study coordinators. The Patient Accrual Report and Forms/Materials Over Due List will be sent to all participating institutions each month.

6.5 QUALITY CONTROL

6.5.1 Initial Training. The Principal Investigators and Study Coordinators of each participating center will attend an initiation/training session conducted by the P.I. of the lead center and the DCC. This session will be held at UCLA and will include a detailed review of the study protocol, study procedures, data collection forms, duties of the Study Coordinator, the procedures for handling blood specimens, etc. It is mandatory that at least one representative from each participating institution complete the training before randomization can begin.

6.5.2 Guidelines for Continuing Review and Auditing of the Clinical Data. Once the clinical center has satisfactorily completed its training and randomization begins, each center will be visited at least once a year by an experienced member of the DCC, who will audit compliance with protocol guidelines for routine procedures such as informed consents, concordance between data forms and the medical chart, and other procedures associated with quality control. This will include adherence to safety monitoring criteria and quality assurance according to guidelines adopted by the NHLBI Monitoring Unit Standard Operating Procedures as applied to cooperative groups. The Data Monitoring and Quality Assurance Guidelines for this study are adopted from NIH publications, entitled Investigator's Handbook - A Manual for Participants in Clinical Trials of Investigational Agents.

Quality Assurance monitoring for essential study procedures and outcomes will be handled by the Core Programs including the Pulmonary Function Testing Core, Radiology Core, Pharmacy Core and the Blood Processing Core. These Core programs will prepare independent manuals of operation and monitor quality features of every study performed. An initial and a follow-up site visit to each participating site will be scheduled by the PFT and Radiology Cores to assure that training, staff and instrumentation are in place and being properly used to collect these outcome measures.

6.5.3 Protocol Compliance. Confirmation of diagnosis and eligibility criteria by central review will be done prospectively, so that any failure of protocol adherence can be detected early. The Data Monitoring and Quality Assurance Guidelines protocol team will review case report forms to establish whether dose adjustments have followed protocol guidelines, and whether appropriate study tests have been obtained. The DCC Staff will also review each case to determine eligibility, availability and validity of data and toxicity assessment. This

review will be conducted on a blinded basis without the review team knowing the randomization assignment of each subject. All of these assessments are performed through review of submitted case report forms after on-site review.

6.5.4 Components of the Quality Assurance Program Implemented for this Multi-center Trial.

6.5.4.1 Monitoring: 1) To monitor the overall progress of the study, to ensure that projected accrual goals are met in a timely fashion, and excessive accrual is avoided; 2) To assure that eligibility and availability rate do not fall below acceptable standards; 3) To assure that risks of the study do not outweigh benefits. Poor performance in any of these areas is cause for concern. Since these activities are performed during study execution, they should lead directly to improved conduct of the trial as problems are identified.

6.5.4.2 The on-site auditing program: The purpose of site visit audits includes: 1) Verification of data accuracy by comparison of the primary medical record with the case report form maintained by the research base for analysis; 2) Verification of the presence of an IRB-approved consent form signed by the subject prior to the initiation of protocol therapy; 3) Verification of IRB approval (and at least annual review and approval) of each sponsored study; 4) Verification that procedures for medication accountability meet the requirements of protocol.

6.5.4.3 Outline of audit procedures: All audits will be conducted by auditors knowledgeable with regard to clinical trials methodology and the protocol. Audits will be randomly timed, will be shortly after the initiation of the study for all clinical centers; subsequent audits will be considered at the problem centers.

6.5.4.4 Data accuracy: The importance of verifying the accuracy of the basic data elements used in the analysis of study endpoints is obvious. Data accuracy is assessed during on-site audits by comparison of the research record (e.g., flow sheets) with the primary patient record. Response assessment may be evaluated by examination of HRCT scans or PFT records, where relevant.

7. STATISTICAL CONSIDERATIONS

7.1 RANDOMIZATION

The statistical design is a 150-subject multi-clinic stratified randomized double blind study with two active treatment arms and randomization at 12 clinics. Clinic is a pre-randomization stratification factor. Patients will be randomly assigned within clinic to one of two treatment groups in a 1:1 ratio. The random permuted block design has been implemented to carry out the randomization using our standard random number program. Block size will be 4 or 6 carried out in a random way and separately for each clinic. Randomization and treatment assignment will be verified and coordinated by the UCLA Data Coordinating Center.

7.2 STATISTICAL CONSIDERATIONS

7.2.1 Primary hypothesis and endpoints: The course of FVC in patients with active SSc-ILD, defined by the presence of "any ground glass opacification" on thoracic HRCT and restriction on PFTs, will be significantly more responsive over a 2-year period to therapy with MMF administered twice daily for two years than to therapy with oral CYC administered once daily for one year (followed by placebo CYC for the second year) ***and*** treatment with MMF will be associated with significantly less toxicity than therapy with CYC.

7.2.2 Primary endpoint:

• %-predicted FVC at 24 months*

*(note that Adverse and Serious Adverse Events will be thoroughly assessed but not as independent efficacy endpoints)

7.2.3. Secondary endpoints:

• TLC, D_LCO, D_LCO/V_A, HRCT visual fibrosis score, TDI, SHAQ, Rodnan skin score

• A composite outcome encompassing FVC, TLC, HRCT-fibrosis score and TDI

• %-predicted FVC and all other endpoints over the intervals 18-24 months, 12-24 months, and between 6-24 months.

7.2.4 Exploratory endpoints:

• SGRQ, SF-36 and health utilities at 24 months.

• HRCT quantitative fibrosis scores at 24 months.

• Subgroup analysis of subjects with %-predicted FVC <70%.

• Dichotomized %-predicted FVC measurements as improved versus not-improved

• Ancillary biomarker studies and others developed by the Steering Committee

7.3 SAMPLE SIZE

7.3.1 Sample size for primary endpoint. The difference in %-predicted FVC between the two treatment arms at 24 months, adjusted for baseline FVC and HRCT-measured fibrosis score, is assumed to be 4%. This was based on the minimal assumption that MMF will be as effective as CYC during the first 18 months (point of maximal %-predicted FVC in response to CYC), that continued treatment with MMF will at least maintain FVC at this value, and that the 1-year treatment with CYC will result in a return to placebo values by 24 months. If subjects treated with MMF continue to improve between 18-24 months, then the sample size requirement will be less, although this is not assumed by the current modeling.
The primary analysis will utilize a robust joint model [23,22,96,32] for longitudinal measurements of %-predicted FVC (6 – 24 months) and based on this model and the data from SLS I we estimate the standard deviation (σ), the time to treatment failure or death and the time to disease- or treatment related dropout. The joint model is able to make valid inference on treatment effects at the longitudinal endpoint in the presence of non-ignorable missing data in %-predicted FVC.

Sample size calculation parameters using the robust joint model

$\Delta=\mu_{MMF}-\mu_{CYC}$	σ	α	Power 1-β	Total n
4.0	8.2	0.05	0.80	132

Final Estimate of Sample Size: We have decided to use a sample size of n=150 patients in order to be conservative, in case of unexpected events or higher-than expected dropouts, even though all 3 methods have built into the model and computation 15% missing data at 24 months.

7.3.2 Sample size for TLC, TDI, Fibrosis Score, Skin Score

The effect size at 24 months and between 6-24 months for the secondary outcomes is expected to be no smaller than for %-predicted FVC at 24 months as the time-trend data for TDI and %-predicted TLC also declined after 18 months in a similar fashion with CYC in SLS I.

7.3.3 Interim analysis, futility, modified power. The trial may be stopped for several reasons: 1) excessive toxicity; 2) demonstration of efficacy; 3) Futility (conditional power) too low for eventual efficacy. The DCC will provide the blinded data in such a way that (2) and (3) above are not compromised. These will be interim analyses at fixed times per the DSMB. The p-value for efficacy stopping will be the Peto-Haybittle boundary, p=0.001. This will ensure that C=0.047 will be the type I error at the final analysis. Futility stopping will be considered by the DCC, CCC, and DSMB.

7.4 STATISTICAL ANALYSIS

7.4.1 Statistical analysis for the primary endpoint: The primary analysis is based on the joint model (defined in section 7.4.5) with 24-month treatment comparison between the CYC and MMF arms. This model will have a random intercept and random slope. Two or more knots may be included in the time effect and an additional random slope might be needed. Additionally, a random effect for site will be included in the joint model.

7.4.2 Secondary analysis of primary endpoint: When the non-longitudinal context is considered again, the statistical approach is a covariance analysis with endpoint %-predicted FVC24 and the covariates baseline %-predicted FVC and HRCT-measured baseline fibrosis in an appropriate statistical model for the relation of the expected value of %-predicted FVC at 24 month to the covariates. Mixed model multiple imputation will be the missing data model (MAR) and the data analysis will use the Huber M analyses.

7.4.3 Statistical analysis for TLC, TDI, Skin Score, HAQ: The primary statistical analysis for %-predicted TLC will follow the approach outlined for %-predicted FVC. The same type of secondary analyses will be used. The approach to TDI at 24 months for the total focal score will be a mixed model with multiple imputation with the covariate fibrosis score. Baseline values of each of these endpoints will be used as a covariate (%- predicted TLC at 24 months = %-predicted TLC at baseline, etc., except for the TDI, which already takes the BDI into account). A modification of the joint model will be used for ordinal outcomes (TDI)

measures. Additionally, several formulations of the skin score over time will be modeled (total skin score at a give time, limited disease skin score and diffuse skin score).

7.4.4 SF-36. The SF-36 primary analysis will attempt to validate the two scales in the exploratory analysis that were promising (via an ordinal joint model analysis). Also, exploratory analyses of the remaining scales will be carried out.

7.4.5 Robust joint model. The robust joint model is comprised of two linked sub-models: a linear mixed-effects sub-model for the longitudinal measurements and a cause-specific hazards sub-model for the competing risks failure time data.

The linkage between the two aspects is modeled through the association between random effects. To be more specific, the model is characterized in terms of the following two components:

$$\begin{cases} Y_i(t) = X_i^{(1)}(t)^T \beta + \tilde{X}_i^{(1)}(t)^T b_i + \varepsilon_i(t), & (1) \\ \lambda_k(t; X_i^{(2)}(t), u_i, \gamma_k, \nu_k) & for \quad k = 1, \ldots, g \\ = \lambda_{0k}(t) \exp\{X_i^{(2)}(t)^T \gamma_k + \nu_k u_i & (2) \end{cases}$$

In the linear mixed effects sub-model (44), Y_i (t) is the longitudinal outcome measured at time (t) for subject i, where i = 1,2,…,n, and n is the total number of subjects in the study. The vectors $X_i^{(1)}$ (t) and $X_i^{(1)}$ (t) are associated covariates and are allowed to change over time. The parameter β represents the fixed effects of $X_i^{(1)}$ (t) and the vector b_i is a latent random variable which can be interpreted as subject-specific effects of $X_i^{(1)}$ (t). Instead of assuming $\varepsilon_i(t) \sim N(0,\sigma^2)$, we propose ε_i (t)~t(0,σ^2, κ), for all t's, where κ represents the degrees of freedom. In addition, we assume that b_i is orthogonal to ε_i (t) and that ε_i (t_i) is orthogonal to ε_i (t_2) for any $t_i \neq t_2$.

Each subject may experience one of g distinct failure types or could be right censored during follow-up. Let T_i be the failure/censoring time, and D_i takes values from {0,1,…, g}, with $D_i = 0$ indicating a censored event and $D_i = k$ showing that the subject i fails from the k th type of failure, where k = 1,…, g. Throughout, the censoring mechanism is assumed to be independent of the survival time. Dependent (or informative) censoring can be treated as one of the g types of failures. Sub-model (23) specifies the distribution of the competing risks survival data with λ_k (t; $X_i^{(2)}$(t), u_i, γ_k, ν_k) being the instantaneous rate for failures of type k at time t given the vector of covariates $X_i^{(2)}$ (t) and the frailty u_i in the presence of all other failure types. The slope and intercept parameter are regarded as random effects in the model.

The hazard model is an extension of the cause-specific competing risks hazards model of Prentice et al (65) in which we introduce subject specific random elements to model the correlation between different failure types. The estimation of this model is by maximum likelihood method using the EM algorithm.

We will apply multiple imputations and estimate adjusted means and their standard error by Huber M regression. Such means have the MAR property, but not the non-ignorable property.

7.4.6 Safety assessment and analysis. Adverse events (AEs) and serious adverse events

(SAEs) will be enumerated in detail in weekly and other periodic reports. AEs and SAEs will also be shown by organ site, with special attention to hematologic events. The toxicity grade of the AEs and SAEs will be presented using a ranking method of analysis, provided the DSMB concurs. The AE and SAE data will also be given cumulatively; when applicable for the DSMB, Poisson regression will be applied to assess differences by treatment group. The 24-month analysis of AEs and SAEs by site, organ system involvement, etc. will be carried out by Poisson regression analysis to compare event rates between the treatment groups.

8.0 STUDY ADMINISTRATION AND OVERSIGHT

The overall administration and management structure for the study is outlined in **Figure 2**.

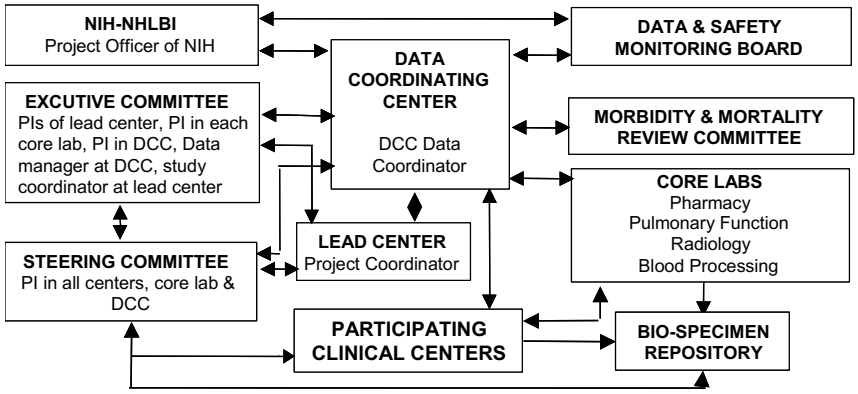


Figure 2: The NIH/NHLBI will appoint a DSMB to review and monitor study design, protocol, enrollment, safety and outcome issues. The UCLA DCC will act as the primary interface between the conduct of the study and its oversight by the sponsor and DSMB. The DCC will appoint a MMRC to assist in adjudicating the cause and relationship of SAE's and deaths to the study protocol. A lead clinical center, also referred to as the CCC, an Executive Committee and a Steering Committee will assist the DCC in its interface with the clinical management of the study, data collection, and oversight of the clinical centers & Cores.

8.1 DATA COORDINATING CENTER (DCC)

The DCC plays a pivotal role in the design, implementation, execution and administration of the study. The DCC will be responsible for randomization, data forms and online reporting systems, preparation of the manual of operations, addressing questions regarding protocol issues, data screening, entry and analysis, monitoring recruitment, follow-up and adherence to protocol, and scheduling and arranging meetings of the Steering Committee, as well as the monthly conference calls. The DCC will collect information from all aspects of the study, including the independent Morbidity and Mortality Review Committee (MMRC), and present interim study results to the NIH/NHLBI and the DSMB. The DCC will also evaluate sites for meeting performance goals and distribute study-related reimbursements to individual centers based on their performance. The DCC will be located in the Department of Biomathematics at UCLA under the direction of Robert Elashoff, PhD.

8.2 EXECUTIVE COMMITTEE

The Executive Committee, chaired by Donald P. Tashkin, M.D., will meet weekly and interact closely with the DCC, the Lead Clinical Center and the Steering Committee to administratively direct and monitor the progress of the clinical trial and to respond to any design, implementation or administrative issues that arise during the study. The Executive Committee will set the agenda for the Steering Committee meetings as a mechanism to disseminate and collect essential information, and to implement modifications related to clinical trial. Other members of the Executive Committee include the key Pulmonary and Rheumatology

Investigators from the Lead Center, the Director of the DCC, and ad hoc representation from the Directors of the Radiology and Pharmacy Cores as needed.

8.3 STEERING COMMITTEE

A Steering Committee chaired by the P.I. (Dr. Tashkin) will provide overall scientific direction for the trial. Voting members will include the Chairman, one Pulmonary and one Rheumatology investigator from each Clinical Center and the DCC Director. The Steering Committee will be responsible for developing a final protocol and Manual of Operations; approving any changes in these; monitoring recruitment and follow-up at each center; and presenting/publishing results from the trial. The Committee will meet face-to-face at least once prior to the initiation of the trial and at least annually for the duration of the trial. Steering Committee members will also participate in monthly conference calls for the duration of the trial. The Steering Committee will have the following subcommittees: Drug Distribution; Monitoring for Drug Safety; Recruitment and Patient Issues; Quality Control for Spirometry, Lung Volumes and D_LCO; HRCT Interpretation; Publications and Presentations; and Ancillary Studies. These subcommittees will schedule conference calls as necessary, and meet as necessary in conjunction with the scheduled Steering Committee meetings.

8.4 LEAD CLINICAL CENTER (CLINICAL COORDINATING CENTER, CCC)

The Lead Clinical Center at UCLA will play a special role in the development, training, implementation and quality assurance monitoring of clinical aspects of the study including the development of IRB and consent templates, CRFs, advertising documents, group training and, together with the DCC, conducting site visits to verify the appropriate conduct of the study at all participating centers.

8.5 STUDY CORES

Four centralized core programs, all situated at UCLA, will support the study including a Pulmonary Function Testing Core, Radiology Core, Pharmacy Core and Blood Processing Core. These Core programs were established in order to provide direct administrative oversight, quality assurance, and standardization related to these essential study processes.

8.5.1 PFT Core. The PFT Core center will be responsible for preparing the PFT manual of operations and for assuring satisfactory standardization and quality of PFT tests performed at all clinical centers. The PFT Core will review and certify all PFT laboratories and technicians at all of the participating clinical centers. The PFT Core will also review all patient test results for completeness, compliance with protocol requirements, and accuracy.

8.5.2 Radiology Core. The Radiology Core will be responsible for establishing and overseeing the CT imaging protocol at each of the clinical centers and for the quantitative image analysis, statistical analysis and preparation of regulatory agency reports of the imaging component of this study.

8.5.3 Pharmacy Core. The Drug Information Center (DIC), Department of Pharmaceutical Services, University of California Los Angeles Ronald Reagan Medical Center will serve as the central drug packaging and distribution site for the 12 participating institutions. Responsibilities include drug procurement and storage, patient randomization, drug

manufacturing, packaging and dispensing, drug accountability, and participating in sponsor site visits and regulatory audits.

8.5.4 Blood Processing Core. The UCLA Blood Processing Core will receive blood samples from participating sites that have been collected in CPT blood processing tubes and prepare purified peripheral blood mononuclear cells that are aliquoted and cryopreserved in a manner suitable for (flow cytometry) analysis. These samples will be stored in liquid nitrogen and then shipped in batches to the Rheumatology Division research laboratory at UT Medical School in Houston for longer-term storage.

8.6 CLINICAL CENTERS

The 12 participating centers constitute a multi-centered group of committed, experienced, and effective clinical researchers with a leading Pulmonologist and a leading Rheumatologist versed in SSc-ILD at each site who will implement all aspects of the clinical protocol, recruit and manage all study participants, and record and report all study data. The 12 original participating sites and replacement sites added during the course of the study are listed as follows:

David Geffen School of Medicine at UCLA*	*Los Angeles, CA*
Boston University, School of Medicine	*Boston, MA*
Feinberg School of Medicine, Northwestern University	*Chicago, IL*
Georgetown University School of Medicine	*Washington, DC*
Johns Hopkins University School of Medicine and The University of Maryland	*Baltimore, MD*
Medical University of South Carolina	*Charleston, SC*
University of California, San Francisco, School of Medicine	*San Francisco, CA*
National Jewish Health / University of Colorado,	*Denver, Colorado*
University of Illinois at Chicago, College of Medicine	*Chicago, IL*
Robert Wood Johnson Medical School at Rutgers [formerly known as University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School]	*New Brunswick, NJ*
University of Michigan Medical School	*Ann Arbor, MI*
University of Texas Medical School at Houston	*Houston, TX*
University of Utah**	*Salt Lake City, UT*
University of Minnesota**	*Minneapolis, MN*

* Also serves as Clinical Coordinating Center and Data Coordinating Center
** University of Utah was added in 2011 to replace Boston University in the recruitment of new subjects. University of Minnesota was added in 2012 to replace National Jewish Health and the University of Illinois at Chicago in the recruitment of new subjects.

9.0 MANAGEMENT OF ETHICAL ISSUES

The investigators will ensure that the study is conducted in accord with the principles of "Good Clinical Practice" and in full conformance with the FDA standards for human subject research as specified in 21 CFR part 312 (Responsibility of Sponsors and Investigators), 21 CFR part 50 (Protection of Human Subjects), and 21 CFR part 56 (Institutional Review Boards), as well as in a manner complaint with Federal HIPAA Guidelines.

9.1 PROCESS OF INFORMED CONSENT

It is the responsibility of the named study investigators at each participating study site to assure that all study participants undergo an appropriate process of written informed consent that has been reviewed and approved by their local Institutional Review Board. The investigators will inform all subjects as to the nature, aims, duration, potential hazards, and procedures to be performed during the study and that his/her medical records and study-related documents may be reviewed by the FDA, NIH or sponsoring companies in a manner designed to protect their confidentiality. This protocol must receive approval by the Institutional Review Board at each participating site prior to implementation of the study at that site. Investigators must also disclose to participants any existing conflicts of interest and explain that patients are completely free to refuse to enter the study or to withdraw from it at any time without prejudice to their medical care. The protocol will be discussed in detail with all potentially eligible patients and the essential components of the informed consent process personally confirmed by a responsible investigator before the consent is signed and countersigned. All revisions of the protocol must be reviewed by the IRB and reflected in the consent form. Patients will receive copies of all consent documents and HIPPA forms for their records and these documents will detail emergency contact numbers for the study and independent reporting numbers for the local IRB in the event that they have any concerns or questions about the process of consent or the handling of human subjects.

9.2 CONFIDENTIALITY OF STUDY DOCUMENTS AND PATIENT RECORDS

The investigators and study staff will assure that all records will be kept confidential to the extent permitted by law. The site Principal Investigators and the Data Coordinating Center will keep a separate log of patients', codes, names, and addresses which are not released or used for routine study management. All study reports and patient samples will be identified only by an assigned coded number to maintain patient confidentiality. Documents which identify the patient by name (informed consent) will be kept in strict confidence.

9.3 FINANCIAL RESPONSIBILITY

The costs of the study medication and laboratory testing (blood and urine) for monitoring potential study drug toxicity and the costs of attending the study center at each of the study visits will be paid for by the study. The high resolution computed tomography (HRCT) scans of the chest that are performed at the beginning and end of the 2-year study and the pulmonary function tests performed at the beginning of the study and every three months for the duration of the study are considered standard clinical practice for the assessment of scleroderma lung disease and will be billed to the patient’s medical insurance company. However, if their medical insurance refuses to pay for the cost of these procedures, these costs will be covered by the study. Other medical expenses that patients may incur as part of the routine management of their scleroderma or other medical conditions will not be paid for by the study.

9.4 EMERGENCY CARE AND COMPENSATION FOR INJURY

If participants are injured as a direct result of research procedures not done primarily for their benefit, they will receive treatment at no cost. The participating institutions do not normally provide any other form of compensation for injury.

10.0 PROCEDURE FOR PROTOCOL MODIFICATION

Modification which may affect the safety of the study patient, or which may alter the scope of the investigation, the scientific quality of the study, the study design, dosages, duration of therapy, patient assessments (added evaluation that poses potential risk or inconvenience to the patient), number of patients, and/or patient eligibility criteria, may be made only after appropriate consultation between the investigators, the sponsor (NHLBI) and the DSMB. Individual sites may not alter the protocol without advanced consultation and approval as noted here-in.

If the consensus is to revise the current protocol, a formal List of Changes will accompany the amended protocol and these will be submitted to the FDA, the site's IRB, and other committees as required. Protocol changes will not be implemented until they have been reviewed and approved by all appropriate regulatory agencies and the study participants notified and/or their consent re-obtained as indicated by the nature of the requested change.

11.0 CONDITIONS FOR EARLY TERMINATION

The investigators and/or sponsor reserve the right to terminate the study at any time. If this becomes necessary, appropriate procedures for continuing long-term follow-up and assuring the adequate treatment and safety of the participating subjects will be arranged after review and approval by the study sponsor, Institutional Review Boards and the FDA.

The DSMB that has been appointed by the NIH/NHLBI will also provide external oversight concerning the safety and scientific integrity of the study for the duration of the clinical trial. The DSMB will review the progress of the study toward meeting enrollment goals, adverse and serious adverse event profiles, and study outcome measures at regular intervals to occur at least twice annually. The DSMB, in consultation with the study sponsor and participating sites may determine at any time that the study should be terminated due to toxicity and/or futility considerations. The final decision of the DSMB to terminate the study, if based on toxicity, is final and agreed to be binding in advance by all parties.

12.0 HANDLING OF SOURCE DOCUMENTS, CASE REPORT FORMS AND REGULATORY DOCUMENTS

The investigators will maintain complete and adequate copies of all source documents, case report forms and regulatory documents so that the conduct of the study can be fully documented and monitored. Case Report Forms will be utilized and completely filled out for each patient entered into the study with copies maintained at the study site and by the UCLA Data Coordinating Center. Study participants will NOT be identified by name on any case report forms. Copies of protocols, case report forms (CRFs), test result originals, all product accountability records, correspondence, FDA filings, IRB filings and responses, patient informed consent, and any other documents relevant to the conduct of the study will be kept on file by the investigator for fifteen years after completion or termination of the protocol. Study documents will not be destroyed, and access to complete study patient records, provided that patient confidentiality is maintained, will be available in the case of inspections by internal quality assurance, the study sponsor and FDA.

13.0 BIOLOGIC SPECIMEN REPOSITORY

The study will bank serum, plasma, buffy coat, peripheral blood RNA and purified peripheral blood mononuclear cells from all study subjects at baseline, after 1 yr of therapy with CYC or MMF, and at the end of the trial. Skin biopsies will also be obtained on a voluntary basis from consenting participants at baseline and after completing the 2 yr protocol. Most specimens will be processed/cryopreserved on site, while fresh blood will be shipped overnight to UCLA where a core will isolate and preserve purified peripheral blood mononuclear cells. All specimens will then be forwarded to Rheumatology Divison research laboratory at UT Medical School in Houston and stored as part of an established SSc repository under the control of Dr. Maureen Mayes. Dr. Mayes will perform the autoantibody tests that are now included as a part of SLS II (Smith, RNP, SS-A/SS-B, Scl-70 and RNA polymerase) and, under the direction of the SLS II Executive and Ancillary Studies Committee, she will distribute samples to other investigators. Requests for biologic samples must be received in writing and reviewed by the Ancillary Studies Committee for scientific approach and value. The Executive Committee, with recommendations provided by the Ancillary Studies Committee, will oversee all requests (both internal and external to the study) to access these samples for ancillary studies. To date, studies that have been proposed on a preliminary basis by interested investigators include cytokine/chemokine analyses, autoantibodies, antibodies to platelet derived growth factor receptor, KL6, surfactant-related proteins, tenascin, circulating progenitor cells (fibrocytes, endothelial cells, stem cells), and immunohistochemistry and microarray analysis for TGF-β signaling pathways. The Biological Samples Repository will not ship specimens without verification that the request has been approved by the SLS II Executive Committee and by the IRB from the requesting site. No personal identifiers will be provided with the samples, although coded demographic and study outcome measures may be provided.

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15.0 SAMPLE INFORMED CONSENT FORM

(to be modified at each participating site as directed by their institutional IRB)

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David Geffen School of Medicine at UCLA
Department of Medicine, Division of Pulmonary & Critical Care

CONSENT TO PARTICIPATE IN RESEARCH

Lay Title: A study comparing mycophenolate to cyclophosphamide in people with interstitial lung disease related to scleroderma

Technical Title: Mycophenolate vs. Oral Cyclophosphamide in Scleroderma Interstitial Lung Disease

Principal Investigator: Donald Tashkin, M.D.
Co-Investigators: Michael Roth, M.D., Philip Clements, M.D, Daniel Furst, M.D., Dinesh Khanna, M.D.

INTRODUCTION

You are being asked to take part in this study because you are at least 18 years of age, and have had scleroderma for less than 7 years with evidence of lung involvement (such as shortness of breath). This study will look at the safety and effectiveness of mycophenolate mofetil compared to cyclophosphamide in people with interstitial lung disease related to scleroderma. Mycophenolate mofetil has been approved by the U.S. Food and Drug Administration (FDA) to prevent organ transplant rejection. Cyclophosphamide has been approved by the FDA for use in cancer treatment. Neither drug has been FDA-approved for the treatment of scleroderma-related lung disease, and therefore both drugs are experimental in this study. This study is sponsored by the National Institutes of Health (NIH).

This consent form contains information that will be discussed with you about the purpose of this study, how your participation may benefit you, the risks of your participation, and what is expected of you. You should read this form and ask about anything you do not understand before deciding whether or not to participate. Once you understand the study, and if you wish to participate, you will be asked to sign this consent form. You will be given a copy to keep.

Your participation in this research study is entirely VOLUNTARY, and you may choose not to participate, or choose to withdraw at any time for your own reasons without penalty or prejudice to your continued medical care at UCLA.

This study will enroll 150 people at 12 research centers, about 20 of whom will enroll at UCLA. Participation requires about 28 visits over about 2 years.

DISCLOSURE

Your health care provider may be an investigator for this study, and as an investigator, is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way associated with this project. You are not under any obligation to participate in any research project offered by your doctor.

Dr. Roth has received payment for consultant services from Hoffman-La Roche, a company supplying some of this study's medication.

PURPOSE OF THE STUDY

The purpose of this study is to look at whether mycophenolate is better (and associated with fewer side effects) than cyclophosphamide in preventing lung damage from scleroderma from getting worse.

PROCEDURES

If you agree to participate in this study and sign this form, there are several procedures that you will be asked to undergo. These are described below, and a chart is included on the last page.

Treatment Groups

If you qualify and decide to join the study, you will be randomly assigned (like the flip of a coin) to one of the following two groups:

- Mycophenolate, target dose 1.5 gram twice daily as tolerated
- Cyclophosphamide, target dose 2 milligrams per kilogram once daily (the dose depends on your weight) as tolerated

'Target dose' means that we will aim to have all participants in each group on this dose of the drug. However, different people react differently to drugs, so we may have to adjust some participants' dose. You have an equal (50/50) chance of being in either group. You will also be given placebo tablets to take with your active medication. A placebo is a pill that looks like the study drug, but has no active medication, and will make it so that neither you nor the study doctor will know which study group you are in. However, this information can be obtained if there is an emergency or if it is necessary to know for your health. You won't start the study taking these doses; rather your dose will be titrated up (slowly increased) to the doses indicated above. People in the mycophenolate group will receive active drug for 2 years. People in the cyclophosphamide group will receive active drug for 1 year, followed by placebo for 1 year.

Vitamin D Sub-Study

You may be offered participation in a sub-study of Vitamin D levels, which would require one additional blood sample (approximately 2-3 tablespoons) at each 3-month visit. If you wish to participate, you will sign a separate consent form. The blood will be stored in a repository for use in several different types of research tests designed to provide information about the causes of scleroderma and the mechanisms by which it involves the skin and the lungs as done at baseline, 1-year, and 2-year study.

Screening Visit

This visit will help determine if you qualify for the study. At this visit, the following will take place:

- You will review your medical and medication history with the study doctor.
- You will have a physical exam in order to assess the extent of your scleroderma.
- You will undergo pulmonary function tests, which measure how much air your lungs can hold and how well you can blow it out. You will blow forcefully into a tube several times. You may be able to skip this procedure if you have undergone this testing within the preceding 40 days.
- You will give a blood sample (approximately 4 tablespoons drawn from a vein in your arm) and urine samples for routine lab tests, and a pregnancy test if you are a woman who is able to become pregnant.

If these tests and procedures indicate that you qualify for the study, you will also undergo a high resolution CT (HRCT) scan of the chest. This scan is similar to an X-ray. You will lie still on a table that moves into a large donut-shaped machine and you will be asked to hold your breath at certain times. A computer will then provide us with very detailed views of your lungs. The process will take 30 minutes to an hour, and can take place on the same or a different day than the rest of your Screening visit.

Baseline Visit

You will return to the clinic within 40 days of your first visit for Visit 2. At this visit, the following will take place:

- You will review any changes in your health or medication with the study doctor, and answer questions about your symptoms.
- You will complete a computer-assisted questionnaire that will assess your ability to function and how short of breath you are. You have the right to refuse to answer any question you do not wish to answer.
- You will complete the health questionnaires, regarding your shortness of breath, your ability to function, and how you rate your quality of life in respect to scleroderma and your lung problems. These questionnaires will take 25-35 minutes to complete. You have the right to refuse to answer any question you do not wish to answer.
- You will complete a questionnaire addressing any gastrointestinal symptoms you may be experiencing (such as nausea or constipation). This questionnaire will take about 10 minutes to complete. You have the right to refuse to answer any question you do not wish to answer.
- You will undergo pulmonary function tests.
- You will give a blood sample (approximately 2-3 tablespoons) drawn from a vein in your arm) that will be stored in a repository for use in several different types of research tests designed to provide information about the causes of scleroderma and the mechanisms by which it involves the skin and the lungs.
- You may undergo one punch biopsy. A punch biopsy is the removal of a small piece of skin (4 millimeters) using an instrument like an apple corer. The area will be numbed before the procedure using local anesthetic, and covered with a simple dressing (like a Band-Aid) afterward. It will not require any stitches. **This procedure is optional**, which means that you can choose to skip this procedure and still be in the rest of the study.
- You will have pregnancy test if you are a women who is able to become pregnant.

If you are eligible for the study, you will be randomly assigned to one of the study groups indicated above and given the medication to take home with you. Because some test results may not be available immediately, this may not occur the day of your visit. If this is the case, the medication will be mailed to you or you can come to the clinic to pick it up.

Regular Interim Visits

There are a number of potential side effects of the study drugs that may be detected only through regular blood and urine testing. Therefore, you will be required to attend a clinic to give regular blood (1 ½ - 3 ½ teaspoons) and urine samples for routine lab tests (and pregnancy tests if applicable) throughout the study. These samples will be collected **every 2 weeks for the first two months and every month for the remainder of the study**. Based on your tolerance of the medication and the results of this laboratory testing, your dosage of medication may be adjusted.

Extra Interim Visits (if needed)

If you should get a side effect that requires adjustment to your dose of study medication, you will be required to attend the clinic to provide blood and urine samples for routine lab tests every 1-2 weeks until the proper dose is achieved.

Three-Month Visits

You will return to the study doctor after you have been on the study medication for 3 months, and every 3 months thereafter for a total of 2 years. At these 3-month visits, the following will take place:

- You will review any changes in your health or medication with the study doctor, and answer questions about your symptoms.
- You will have a physical exam, in order to assess the extent of your scleroderma.
- You will complete the health questionnaires (the questionnaire addressing shortness of breath will be completed only every 6 months).
- You will undergo pulmonary function tests.
- You will give a blood sample (approximately 4 tablespoons) and urine samples for routine lab tests (and a pregnancy test if applicable).

One-Year Visit

In addition to the routine tests that will be done at each of the 3 month visits, the following will take place:

- You will give a blood sample (approximately 2-3 tablespoons) that will be stored in a repository for use in several different types of research tests designed to provide information about the causes of scleroderma and the mechanisms by which it involves the skin and the lungs.
- You will complete the health and gastrointestinal questionnaire.

Final Visit

You will return to the clinic 2 years after starting treatment for your final visit. At this visit, the following will take place:

- You will review any changes in your health or medication with the study doctor, and answer questions about your symptoms.
- You will have a physical exam, in order to assess the extent of your scleroderma.

- You will complete the health questionnaires.
- You will complete the gastrointestinal questionnaire.
- You will undergo pulmonary function tests.
- You will give a blood sample (approximately 4 tablespoons) and urine samples for routine lab tests (and a pregnancy test if applicable).
- You will also give a blood sample (approximately 2-3 tablespoons) that will be stored in a repository for use in several different types of research tests designed to provide information about the causes of scleroderma and the mechanisms by which it involves the skin and the lungs. This will be taken at the same time as your other blood sample and will not require an extra needle-stick.
- You will have an HRCT scan.
- You may undergo one punch biopsy. Just as at the Baseline Visit, this procedure is optional.

This visit will mark the end of your study participation, but you may be contacted in the future to find out how you are doing with your scleroderma and lung disease.

Early Discontinuation

If you leave the study early for any reason, you will be asked to continue to return to the clinic every 6 months (at 6 months, for the One-Year Visit, at 18 months, and for the Final Visit (at 2 years) as outlined above. This additional data will help achieve our research goals even if you are no longer taking study drug. You have the right to refuse to complete these visits.

Management of Treatment Failures

If, after the first 3 months of being on study drug, your lung function markedly decreases, you will be asked to stop taking the study drug. If that situation occurs, the study team will work with you and your treating physician to review your medical condition and develop an alternative treatment plan that is independent from this research study. The exact type of treatment that you might receive, including the responsibility for all the medications and testing involved, would be up to you and your treating physician to determine. However, regardless of the type of treatment that you receive after stopping the study drug, we would ask that you return to and complete the previously scheduled visits at 6 months, One year, 18-months, and Final Visit study evaluations as detailed above.

Other Information

We would like to store any leftover blood and tissue (skin biopsy) samples for future lung disease and scleroderma research. Your samples will be labeled with a code, and the only link between that code and your identity will be stored securely in your study doctor's records. Your samples will be stored until they are no longer useful (that is, no more research can be done on them), at which time they will be destroyed.

Long-term follow-up

We would like your permission to follow you for up to 12 years after the study. You will receive an annual phone call for up to 12 years after the study, which will take about 5 minutes. During that call, we will review you health, including any major changes (like having an organ transplant or being treated for cancer), and how scleroderma is affecting your life (like whether or not you need supplemental oxygen therapy, dialysis, or nutrition through a tube).We may also

use medical records and various databases to look for long-term complications of the study drugs. Please indicate by marking one of the boxes at the end of this consent whether you agree to this long-term follow-up.

POTENTIAL RISKS AND DISCOMFORTS

For your safety, you must tell the study staff about all medications you are taking before you start the study, and any changes in your medications while on the study. There may be unknown or unforeseeable risks to participation in the study. It is important that you report any and all symptoms or possible reactions to your study doctor, even if you think it isn't related to your study participation.

For the risks of study drugs noted below, the number in parentheses indicates the percentage of patients in whom the side effects have been seen.

Risks of Cyclophosphamide

The most common side effects reported by people taking cyclophosphamide include:

- Azoospermia (decreased level of sperm, 60-100%)
- Hair thinning (up to 50-60%)
- Amenorrhea (absence of menstrual period, see below for more information, up to 50%)
- Increased risk of infection (30%)
- Nausea (upset stomach), vomiting, and diarrhea (up to 30-40%)
- Blood in the urine (20%)
- Skin rashes (less than 2%)
- Neoplasia (abnormal cell growth, see below for more information, less than 5 %)

Frequent toxicity screening (that is, the monthly blood and urine tests) and appropriate dosage adjustments should minimize the drug's risks.

Special Information for Women: The use of cyclophosphamide in women can lead to fibrosis of the ovaries, which can give rise to irregular periods, the onset of menopause, and loss of fertility (the ability to become pregnant). In women who have already had their menopause, this is not a problem. This problem is most likely to be important to younger women who are still having periods, some of whom may want to become pregnant in the future. **The loss of fertility is usually permanent.**

Special Information about Cancer: The lifetime risk of cancer (neoplasia) is not clear, but is probably less than 5% after 1 year of taking cyclophosphamide (that is, after 1 year of taking cyclophosphamide, you may have up to a 5% greater chance of getting cancer at any point in your life). Although cyclophosphamide is used to treat many cancers or malignancies, its use itself can give rise to other kinds of cancer, particularly of the bladder, the skin and the blood. The appearance of cancer during the first year of cyclophosphamide treatment is unlikely, but the risk of cancers may appear later in life. This means that by taking cyclophosphamide during the study, you may have a higher chance of getting cancer later in life, even after you have stopped taking the study drug.

Risks of Mycophenolate

Risks experienced by patients taking mycophenolate to prevent organ transplant rejection include:

- Urinary tract infection (37%)
- Diarrhea (31%), constipation (23%), and nausea (20%)
- Peripheral edema (swelling of tissues, usually in the lower limbs, 29%)
- Anemia* (low red blood cells, 26%), leukopenia (low white blood cells, 23%), and thrombocytopenia (low blood platelets, 10%)
- Abdominal (belly) pain (25%), fever (21%), headache (21%) and infection (19%)
- Respiratory infection (22%), dyspnea (shortness of breath, 16%), and increased cough (16%)
- Tremor (shakiness, 11%), insomnia (inability to sleep, 9%), and dizziness (6%)
- Skin rashes (8%) and acne (10%)
- Hypokalemia (low potassium in the blood, usually with no symptoms, 9%)
- Gastrointestinal hemorrhage (heavy bleeding from the lining of your stomach or intestines, 3%)
- Rarely, progressive multifocal leukoencephalopathy (PML), a frequently fatal neurologic disorder. However, all of the patients receiving MMF for prevention of transplant rejection in whom PML has been reported were receiving other immunosuppressive therapy at the same time; PML has not previously been reported in patients treated with MMF as the sole immunosuppressive drug for scleroderma lung disease.
- BK Virus has been rarely reported when MMF is used in combination with another immunosuppressive. A large portion of the general population already carries BK Virus with no symptoms, but taking MMF may cause you to develop symptoms, like kidney problems. Three additional viruses are in this family, but have not been directly linked to MMF: KI and WU viruses have been linked to respiratory illness and Merkel cell virus (MC virus) may be linked to a certain type of skin cancer. While these 3 viruses have not been linked to the use of MMF, they are a theoretical risk of suppressing the immune system.
- Pure red cell aplasia (PRCA): cases of PRCA have been reported in patients treated with mycophenolate in combination with other immunosuppressive drugs (drugs that suppress the immune system). PRCA is a type of anemia in which the bone marrow stops producing red blood cells, and may cause symptoms like paleness, weakness, and tiredness.

*Anemia may cause easy fatigue or loss of energy; rapid heartbeat, shortness of breath, and headache especially during exercise; difficulty concentrating; dizziness; and pale skin. The effects of anemia may be reduced with treatment like certain dietary supplements.

Most of the patients in whom the above side effects were seen were receiving other drugs known to be associated with these complications. Few side effects have been reported in patients receiving mycophenolate for scleroderma-related lung disease.

Risks of Breathing Tests

Discomfort is unusual during these breathing tests. However, some people experience temporary shortness of breath, cough, chest discomfort, lightheadedness or fainting, or headache while undergoing these tests. These feelings are usually temporary and resolve on their own. You will

be closely monitored during these tests, and treatment will be available in case you experience any symptoms. If you start to feel any unusual symptoms, please tell the study staff immediately.

Risks of HRCT Scans

During the CT scans you may rarely experience some anxiety due to being in an enclosed space. With regard to potential risks of radiation exposure: we are exposed to radiation on a daily basis, both from natural (sun and earth) and man-made sources. In addition to the radiation that you may be exposed to as part of your clinical care (if you are receiving clinical care), you will receive a maximum of one HRCT scan of the chest in one year of participating in this research study. The estimated radiation dose that you will receive as a result of the additional CT scan is 120 millirem, or 2.4% of the 5,000 millirem annual limit allowed radiation workers.

Risks of Punch Biopsies

The local anesthesia used to numb the area can produce a stinging sensation that lasts for a few seconds prior to the procedure. You may experience minimal pain or bleeding after the procedure.

Risks of Blood Draws

Drawing blood from a vein in your arm may cause some discomfort, bleeding or bruising, and rarely, infection or fainting. A total of 2 ½ to 3 ½ cups of blood will be collected over the course of the entire study.

Risks of Pregnancy

Cyclophosphamide has been reported to cause birth defects and should not be used in pregnancy or in women planning to become pregnant within the next two years or if breast feeding. There have been no adequate studies of mycophenolate mofetil in pregnancy women. However, studies in rats have shown malformations (specifically of the head and eyes) of the offspring of female rats taking mycophenolate mofetil. It is not known whether or not these drugs are excreted in breast milk, but many drugs are. Therefore, pregnant women, women of child-bearing potential who are not employing adequate contraceptive measures, and women who are breast-feeding will be excluded from this study. Women who are able to become pregnant (those less than age 55 who have not been postmenopausal for at least 5 years and who have not had surgery to remove the uterus and/or ovaries) will be monitored with frequent urine pregnancy tests throughout the study.

There may also be other unknown risks of the study drugs and procedures to pregnant women, fetuses, and nursing children. For this reason, women who are able to become pregnant must have negative urine pregnancy tests and agree to use **two acceptable methods** of birth control throughout the study. Acceptable methods of birth control include hormonal contraceptives (oral contraceptive pills, patch, vaginal ring), implantable contraceptives (such as Norplant, levonorgestal IUS), injectable contraceptive (such as Depo-Provera), barrier methods (such as male/female condoms, diaphragm, cervical cap), spermicides (such as vaginal sponge, spermicidal cream, foam or jelly), intrauterine contraceptive devices (IUD), or surgical sterilization (tubal ligation, vasectomy).

The study staff will discuss this with you further. If you think you are pregnant or may become pregnant, you must tell the study doctor immediately. Follow-up information on the outcome of your pregnancy will be requested, such as if there is anything unusual in the progress of your pregnancy or if it ends early. The study doctor may share this information with the sponsor and with the IRB (Institutional Review Board).

ANTICIPATED BENEFITS TO SUBJECTS

You may not receive any specific benefits from participation in this study. However, if mycophenolate or cyclophosphamide is effective in the treatment of scleroderma-related lung disease, then it could be possible that you may receive the benefits of improvement in lung function and possibly even improvement in other internal organ involvement (that is, other organs that have been affected by your scleroderma). There will be no financial charge for the medication.

ANTICIPATED BENEFITS TO SOCIETY

Knowledge gained from this study may help in finding safe and effective treatment plans for scleroderma.

ALTERNATIVES TO PARTICIPATION

You do not have to join this study to receive treatment for your scleroderma. Other treatments that have been proposed for use in scleroderma include cyclosporine (Restasis), azathioprine (Imuran), Relaxin, methotrexate (Trexall), penicillamine (Cuprimine), gamma interferon (IFN-gamma) and photopheresis (a procedure in which your blood is mixed with a drug and exposed to light to active it). However, none of these medications have yet been proven to be effective in treating scleroderma.

You may ask your doctor for any of these treatments, or you may volunteer for another study if you qualify. Before you decide to take part in this study, you may discuss the benefits and risks of available alternatives with the study doctor.

PAYMENT FOR PARTICIPATION

You will not receive payment for participation in this study. Parking at UCLA will be provided for all visits.

POSSIBLE COMMERCIAL PRODUCTS

All tissue and/or fluid samples are important to this research study. Your sample will be owned the University of California or by a third party designated by the University. If a commercial product is developed from this research project, the commercial product will be owned by the University of California or its designee. You will not profit financially from such a product.

INFORMATION ABOUT YOUR SAMPLE

We will not provide you with any information about your sample because the information produced will not be of any practical use to you or your doctor.

FINANCIAL OBLIGATION

The costs of the study medication and laboratory testing (blood and urine) for monitoring potential study drug toxicity and the costs of attending the study center at each of the study visits will be paid for by the study, and you will not be charged.

The high resolution computed tomography (HRCT) scans of the chest that are performed at the beginning and end of the 2-year study and the pulmonary function tests performed at the beginning of the study and every three months for the duration of the study are considered standard clinical practice for the assessment of your scleroderma lung disease and will be billed to your medical insurance company. However, if you do not have insurance or your medical insurance company refuses to pay for the cost of these procedures, these costs will be covered by the study; you personally will not have to pay for these procedures. If you are required to pay for a copayment or deductible in order to obtain these tests, the study will also reimburse you for these expenses upon presentation of appropriate receipts and insurance documents. As a result, even though your insurance will be billed, you will not be held personally responsible for the costs of these tests.

If you are asked to stop from taking the study drug because of continued deterioration of your lung condition, then you and your primary treating physician will become responsible for deciding the best available treatment options and for any subsequent costs involved in your ongoing treatment. However, should you elect to return for the One-Year and Final Visit evaluations, the study will cover the costs required for those evaluations as already detailed.

Other medical expenses that you may incur as part of the regular management of your scleroderma or other medical conditions, which are not specifically described as part of this research study, will not be paid for by the study.

EMERGENCY CARE AND COMPENSATION FOR INJURY

If you are injured as a direct result of research procedures not done primarily for your benefit, you will receive treatment at no cost. The University of California does not normally provide any other form of compensation for injury.

PRIVACY AND CONFIDENTIALITY

The only people who will know that you are a research subject are members of the research team and, if appropriate your physicians and nurses. No information about you, or provided by you during the research, will be disclosed to others without your written permission, except if necessary to protect your rights or welfare (for example, if you are injured and need emergency care), or if required by law.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity. Authorized representatives of the Food and Drug Administration (FDA), the National Heart, Lung and Blood Institute, the NIH, and the UCLA Office for the Protection of Research Subjects may need to review records of individual subjects. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others. All records will be kept in locked locations accessible only to authorized study personnel.

All samples stored for future research will be labeled with a code to protect your identity. Personal identify information, such as name and date of birth, will not be attached to the sample. The Principal Investigator, Dr. Tashkin will maintain the link between the code the personal identifying information. This code will be kept on a password-protected computer in a locked office to which only Dr. Tashkin will have access. Other researchers who may use your samples will not be provided with the link or any personal identifying information.

GENETIC INFORMATION IN YOUR SAMPLE: POSSIBLE LIMITS TO CONFIDENTIALITY

Every blood sample contains genetic information. Recent studies have found normal and disease producing genetic variations among individuals. Such variations may permit identification of individual participants at risk for certain disorders. Despite this possible limitation, every precaution will be taken to maintain your confidentiality now and in the future.

We have learned from past research that we will not always be able to predict future research findings and new technologies. You should be aware that unforeseeable problems might arise from new developments. Possible problems include insurance or employment discrimination based on genetic information.

Within the limits imposed by technology and the law, every effort will be made to maintain the privacy of your genetic information.

PARTICIPATION AND WITHDRAWAL

Your participation in this research is VOLUNTARY. If you choose not to participate, that will not affect your relationship with UCLA (or UCLA Medical Center), or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at UCLA.

CONSEQUENCES OF WITHDRAWAL

You may withdraw at any time and are under no obligation to undergo any other procedures. Withdrawal from this study will not affect or interfere with your routine care.

WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR

The investigator may withdraw you from the study in certain circumstances, even if you would like to continue. The investigator will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

NEW FINDINGS

During the course of the study, you will be informed of any significant new findings, good or bad, such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

IDENTIFICATION OF INVESTIGATORS

In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed below. If you have any questions about the research, please feel free to contact Dr. Tashkin at (310) 825-3163, Dr. Roth at (310) 825-9393, or Drs. Clements, Furst or Khanna at (310) 825-5330. After hours, weekends and holidays the investigators can be reached 24-hours-a-day via the UCLA Operator at (310) 825-6301.

RIGHTS OF RESEARCH SUBJECTS

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you have questions regarding your rights as a research subject, you may contact the Office for Protection of Research Subjects, UCLA, 11000 Kinross Avenue, Suite 102, Box 951694, Los Angeles, CA 90095-1694, (310) 825-8714.

SIGNATURE OF RESEARCH SUBJECT

I have read (or someone has read to me) the information provided in this consent form. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form, as well as a copy of the Subject's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

_____

Name of Subject

_____ _____

Signature of Subject Date

Please initial one of the spaces below to indicate whether you will agree to the optional punch biopsies for the skin repository:

_____ I agree to provide a skin biopsy at the baseline and 24 month visits.

_____ I decline to provide a skin biopsy at the baseline and 24 month visits.

Please initial one of the spaces below to indicate whether we may contact you regarding future research:

_____ I agree to be contacted about future scleroderma studies.

_____ I decline to be contacted about future scleroderma studies.

Please initial one of the spaces below to indicate whether we may contact you annually for up to 12 years after the study:

_____ I agree to be contacted annually for up to 12 years after the study.

_____ I decline to be contacted annually for up to 12 years after the study.

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____
Name of Investigator

_____ _____
Signature of Investigator Date (must be the same as subject's)

Schedule of Events

	Screening Visit	Baseline Visit	Interim Visits	3-month Visits	Final Visit
Medical history	X				
Health and medication review	X	X		X	X
Physical exam	X	X		X	X
Lung function testing	X	X		X	X
Blood and urine sample	X		X	X	X
Questionnaires		X		X	X
HRCT	X				X
Pregnancy test*	X	X	X	X	X
Punch biopsy (optional)		X			X
Vitamin D sub-study (optional)				X	
Blood sample for storage		X		1-yr only	X

* For women who are able to become pregnant.

APPENDIX A CONTRAINDICATED MEDICATIONS FOR CYC and MMF

Activated charcoal	Potaba
Acyclovir	Pentostatin
Allopurinol	Remicade
Amphotericin*	Ritonavir*
Azathioprine	Rituximab
Cholamphenicol	Succinycholine
Cholestyramine	Tamoxifen
Colesavelam	Valacyclovir
Colestipol	Live vaccines administered within 30 days of, or after randomization
Cyclosporine	Bacillus of Calemett and Guerin Vaccine
Digoxin tablets (capsules okay)*	Measles Virus
D-penicillamine	Mumps
Echinacea	Polio Virus
Enbrel	Rotovirus
Ganciclovir	Rubella
Hydrocholothiazide*	Small pox
Humira	Typhoid
Indomethacin*	Varicella Virus
Methotrexate	Yellow Fever
Prednisone ≥10mg/day (or equivalent corticosteroid)	

Medications that require adjustments but subjects may be enrolled if guidelines followed

Pneumococcal vaccine may require booster dosing to assure vaccine is effective*
Influenza vaccine administered after start of CYC or MMF may not be protective*

Hormonal contraceptives may not be effective during administration of MMF and a second type of contraception must be used to participate in study*

- Levongogrestrel
- Norethindrone
- Mestranol
- Norgestrel
- Ethinyl estradiol
- Etonogrestrel

Antacids may not be taken together at the same time with MMF, but may be used if not taken within 2 hrs of MMF dosing*

- Al Carbonate
- Al Hydroxide
- Al Phosphate
- Dihydroxy Aluminum Aminoacetate
- Dihydroxy Aluminum Sodium Carbonate
- Magaldrate
- Mg Carbonate
- Mg Hydroxide
- Mg Oxide
- Mg Trisilic

Iron may not be taken together at the same time with MMF, but may be used if not taken within 2 hrs of MMF dosing*

* denotes drugs likely to be used in this group of SSc patients

FINAL STATISTICAL ANALYSIS PLAN

I. Overview

The primary objective of Scleroderma Lung Study II was to compare CYC and MMF for the treatment of systemic sclerosis-related lung disease. The primary and secondary efficacy endpoints for the study are provided below.

Primary: Course of FVC % of predicted over 24-month study period

Secondary:

- Total lung capacity (TLC)
- Diffusing capacity for carbon monoxide (DLCO)
- Dyspnea (Mahler Transitional Dyspnea Index)
- Health related quality of life (SF-36, Saint George's Respiratory Questionnaire)
- Functional ability (Scleroderma Health Assessment Questionnaire)
- Skin thickness (modified Rodnan skin score)
- Radiographic fibrosis (QLF)

II. Randomization Process

The statistical design was a 2-treatment, multi-clinic stratified randomized double blind study with 14 clinics. Clinic was a pre-randomization stratification factor. Patients were randomly assigned within clinic to one of two treatment groups in a 1:1 ratio. The random permuted block design has been implemented to carry out the randomization using our standard random number program from other NIH funded trials. Block size was 4 or 6 carried out in a random way and separately for each clinic.

III. Sample Size Calculation

A two-sided Z-test was used with α = Prob TYPE 1 error=0.05, Power = **0.85,** corresponding to a specified Δ difference. The number of patients shown is the total number of patients (assuming equal # patients in each group, i.e., $n_1 = n_2$).

The formula for the sample size was:

$$n_1 = n_2 = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\Delta^2}$$

where for $\alpha = 0.05$ and $1 - \beta = 0.85$, $Z_{1-\alpha/2} = 1.96$ and $Z_{1-\beta} = 1.036$ according to the standard normal distribution.

The standard deviation σ is the standard deviation of adjusted %FVC at 24 month for each group (adjusted for baseline %FVC and fibrosis).

μ_{MM}	μ_{CYC}	$\Delta = \mu_{MM} - \mu_{CYC}$	σ	Total $n = n_1 + n_2$	Adjusted for dropout
67.76	66.06	1.7	2.7	92	124 (25% dropout)
68.06	66.06	2.0	3.0	82	110 (25% dropout)

67.76	**66.06**	**1.7**	**3.0**	**112**	**150 (25% dropout)**

The 25% reflects approximately the prior trial experience in SLS I, as the stated σ was inflated to be conservative. Our change of 1.7 for the effect size was very conservative, and our estimate of σ was much larger than that obtained for CYC in SLS 1. The 1.7 value of Δ may be thought of as the minimum Δ that could be obtained with a power of 85%.

IV. Descriptive Analyses

Baseline comparability of the treatment groups for the most important prognostic variables was illustrated using appropriate descriptive statistics. Descriptive statistics including median, mean, standard deviation, and interquartile range were computed to summarize the data for each variable. Graphics such as box-plots and histograms were generated to check for skewness and outliers.

V. Primary Efficacy Analysis

The primary analysis utilized a robust joint model for longitudinal measurements of %-predicted FVC (3 – 24 months). Developed by Dr. Elashoff and colleagues, this inferential model consists of a mixed effects model for longitudinal outcomes and a survival model to handle non-ignorable missing data due study dropout, treatment failure or death (Li N, Elashoff RM, Li G, Tseng CH. Joint analysis of bivariate longitudinal ordinal outcomes and competing risks survival times with nonparametric distributions for random effects. Stat Med 2012;31:1707-21.). The longitudinal model includes pre-specified covariates of baseline FVC % predicted, quantitative extent of lung fibrosis (%) in the lobe of maximal involvement (QLF-LM), as well as a time trend, treatment assignment, and a treatment-time trend interaction. This joint model builds on our experience with data from Scleroderma Lung Study I.

In the regression, the time trend was modeled by piecewise linear splines. Average values of adjusted scores within group were plotted over the same time period.

Sensitivity analyses were also carried out by fitting the joint model for CYC and MMF groups separately and to include the use of proton pump inhibitors as a covariate as this medication may affect absorption of MMF. The model details are provided below.

A. Longitudinal model for FVC % of predicted:

FVC % predicted=$\beta 0 + \beta 1$ FVC0 + $\beta 2$ maxfib + $\beta 3$ Arm + $\beta 4$ Time[3-12m] + $\beta 5$ Time[12-21m] + $\beta 6$ Time[24m] + $\beta 7$ Time[3-12m] *Arm + $\beta 8$ Time[12-21m] *Arm+ $\beta 9$ Time[24m] *Arm + $\eta 1 + \varepsilon$, where:

FVC% predicted0=baseline FVC% predicted
Maxfib= baseline maximum fibrosis quantitative score
Arm=treatment indicator (MMF vs CYC, CYC as the reference group)
Time[3-12m] : time trend for 3-12 months
Time[12-21m] : time trend for 12-21 months
Time[24m]: 24 month value
Time[3-12m]*Arm : time trend difference between MMF and CYC for 3-12 months
Time[12-21m]*Arm : time trend difference between MMF and CYC for 12-21 months

Time[24m]*Arm: 24 month value difference between MMF and CYC
$\eta 1$ = subject random effect in the longitudinal model
ε =measurement error

B. Survival Model for time to event

Hazard function: $h(t)= h0(t) \exp(\alpha 1 \text{ FVC0} + \alpha 2 \text{ maxfib} + \alpha 3 \text{ Arm} + \eta 2)$, where:

h0(t) is the baseline hazard function
Arm=treatment indicator
FVC0=baseline FVC
Maxfib= baseline maximum fibrosis quantitative score
$\eta 2$ = subject random effect in the time to event model

C. Joint Model of Longitudinal model for FVC% predicted and Survival Model for time to event allows the correlation between $\eta 1$ and $\eta 2$ to incorporate the non-ignorable missing data related to time to off treatment, death, or treatment failure.

VI. Secondary Efficacy Analysis

Secondary efficacy endpoints were also analyzed based on similar joint model described above. Baseline values of each of these endpoints were a covariate (i.e., TLC at 24 months=TLC at baseline, etc.). No multiple comparison adjustments were applied to the secondary endpoint analyses.

VII. Safety Analysis

All AEs and SAEs were summarized by counts of subjects with AEs and individual occurrences. Kaplan Meier survival curves were generated for time to death for each treatment group, and the log-rank test was used to compare the two treatment groups. Chi-square test or Fisher's exact test were used to compare the incidence of AEs and SAEs, individually and by organ systems, between the two groups. There were no adjustments for multiple comparisons in the safety analysis.