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

PROTOCOL SUMMARY

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

PRINCIPAL INVESTIGATORS:

<table>
<thead>
<tr>
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</thead>
<tbody>
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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 | Baltimore, MD |
| Medical University of South Carolina    | Charleston, SC |
| University of California, San Francisco, School of Medicine | San Francisco, CA |
| University of Colorado, National Jewish Health | Denver, Colorado |
| University of Illinois at Chicago, College of Medicine | Chicago, IL |
| 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 |

* Also serves as Clinical Coordinating Center and Data Coordinating Center

Protocol Version 2.0 Dated 05/15/2009 (Pg 1 of 8)
| 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)  
Grant #R01 HL089758-01A1 and #R01 HL089901-01A1 |
| 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<sub>L</sub>CO) and the ratio of D<sub>L</sub>CO to alveolar volume (D<sub>L</sub>/V<sub>A</sub>), 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, ages 18-75 years, 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.

1. Age $\geq 18$ and $< 75$ 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 $\geq 2$ on the Magnitude of Task component of the Mahler Modified Dyspnea Index).
4. FVC $< 80\%$ of predicted
5. Onset of the first non-Raynaud manifestation of SSc within the prior 5 years.
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 measured at screening. 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.

**EXCLUSION CRITERIA**

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

1. FVC $< 45\%$ of predicted
2. $D_lCO$ (Hemoglobin [Hbg]-corrected) $< 40\%$ of predicted
3. FEV$_1$/FVC ratio $< 65\%$
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] <4000) or thrombo-cytopenia (platelet count <150,000)

8. Clinically significant anemia (<10g/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 random-
ization.

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 > 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 30 (±10) 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.
   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$_L$CO
   • %-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>
<thead>
<tr>
<th>Table 1. Schedule of Assessments</th>
<th>Months after randomization</th>
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<tr>
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<tr>
<td>General H&amp;P</td>
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<tr>
<td>SSc-H&amp;P, vitals</td>
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<td>Rodnan skin score</td>
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<td>Lung exam</td>
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<td>Mahler Dyspnea</td>
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<td>SHAQ, SF-36, SGRQ, Cough index, SSc pain/global &amp; Health Care Utilization</td>
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<tr>
<td>UCLA SCTC GIT</td>
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<td>Blood for repository</td>
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<tr>
<td>Skin biopsy for repository***</td>
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</table>

*To take place within 7-30 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 in order to participate in study
+ For women of childbearing potential
++ Spot creatinine/protein ratio completed if clinically necessary