# Scleroderma Lung Study III (SLS III):

# Combining the anti-fibrotic effects of pirfenidone (PFD) with mycophenolate (MMF) for treating scleroderma-related interstitial lung disease

**Protocol Identifying Number: UCLA-SLS3**


**Principal Investigator**

Michael D. Roth, M.D.
Division of Pulmonary & Critical Care
Department of Medicine, 43-229 CHS
David Geffen School of Medicine/UCLA
Los Angeles, CA 90095-1690
Tel: (310) 206-7389
Fax: (310) 206-5088
*mroth@mednet.ucla.edu*

**Co-Principal Investigator**

Dinesh Khanna, M.D., M.Sc.
Division of Rheumatology
Dept. of Internal Medicine, Suite 7C27
Univ. of Michigan School of Medicine
300 North Ingalls Street, SPC 5422
Ann Arbor, MI 48109
Tel: (734) 232-2104
Fax: (734) 763-5761
*khannad@med.umich.edu*

**Data Coordinating Center Director / Principal Statistician**

Cathie Spino, D.Sc
Department of Biostatistics
School of Public Health II
University of Michigan
1415 Washington Heights, Rm M4507
Ann Arbor, MI 48109-2029
Tel: (734) 615-5469
Fax: (734) 647-3711
*spino@med.umich.edu*


**IND:** IND# 135848
Michael D. Roth, M.D.
David Geffen School of Medicine/UCLA


**Financial support for an Investigator-Initiated Study provided by:**

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080


**Protocol Version Number: v.2.5**
**Protocol Version Date: 11/17/2021**

## List of Participating Clinical Sites as of June 30, 2020:

(15 to 25 participating sites anticipated)

| Site # | Institution | Location |
|---|---|---|
| 1 | Boston University, School of Medicine | *Boston, MA* |
| 2 | David Geffen School of Medicine at UCLA* | *Los Angeles, CA* |
| 3 | Georgetown University School of Medicine | *Washington, DC* |
| 4 | Harvard Medical School, Brigham & Women's Hospital | *Boston, MA* |
| 5 | Hospital for Special Surgery, New York | *New York, NY* |
| 6 | Johns Hopkins University School of Medicine | *Baltimore, MD* |
| 7 | Medical University of South Carolina | *Charleston, SC* |
| 8 | Northwestern University Feinberg School of Medicine | *Chicago, IL* |
| 9 | Rutgers Robert Wood Johnson Medical School | *New Brunswick, NJ* |
| ~~10~~ | ~~University of California, San Francisco, School of Medicine~~ | ~~*San Francisco, CA*~~ |
| 11 | University of Colorado Denver | *Denver, CO* |
| 12 | University of Michigan Medical School** | *Ann Arbor, MI* |
| ~~13~~ | ~~University of Minnesota Medical School~~ | ~~*Minneapolis, MN*~~ |
| 14 | University of Pittsburgh | *Pittsburgh, PA* |
| 15 | University of Texas Medical School at Houston | *Houston, TX* |
| 16 | University of Utah School of Medicine | *Salt Lake City, UT* |
| 17 | University of Washington School of Medicine | *Seattle, WA* |
| 20 | University of Indiana Heatlh | *Indianapolis, IN* |

*Also serves as Clinical Coordinating Center

**Also serves as Data Coordinating Center

**Table of Contents**

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ACR | American College of Rheumatology |
| ADL | Activities of daily living |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate Aminotransferase |
| ATS | American Thoracic Society |
| AUC | Area under the curve |
| BID | Twice daily |
| BDI | Baseline Mahler Modified Dyspnea Index |
| BAL | Bronchoalveolar lavage |
| BUN | Blood Urea Nitrogen |
| CDC | Center for Disease Control |
| CFR | Code of Federal Regulations |
| CLIA | Clinical Laboratory Improvement Amendments |
| Cmax | Maximum concentration |
| CMP | Clinical monitoring plan |
| CMV | Cytolomegalovirus |
| COVID-19 | Coronavirus Disease 2019 |
| Cr | Creatinine |
| CRF | Case Report Form |
| CRISS | Combined Response index in Systemic Sclerosis |
| CTCAE | Common Terminology Criteria for Adverse Events V4.03-2010 |
| CYC | Cyclophosphamide |
| CYP | Cytochrome P450 |
| DCC | Data Coordinating Center |
| DLCO | Single-Breath Diffusing Capacity of the Lung for Carbon Monoxide |
| DLCO-Hb-% | DLCO, adjusted for age, height, gender and hemoglobin |
| DMARD | Disease-modifying antirheumatic drug |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Forms |
| ERS | European Respiratory Society |
| EULAR | European League Against Rheumatism |
| FEV1 | Forced Expiratory Volume in the first second |
| FDA | Food and Drug Administration |
| FVC | Forced vital capacity |
| FVC-% | Forced vital capacity as a percentage of the age-, height-, gender- and race-adjusted predicted value |
| GERD | Gastroesophageal reflux disease |
| GCP | Good Clinical Practice |
| GGO | Ground glass opacification |

| | |
|---|---|
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| H&P | History and physical |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| Hgb | Hemoglobin |
| HIPAA | Health Insurance Portability and Accountability Act |
| HRCT | High resolution computerized tomography |
| HRCT-TLC | HRCT-measured total lung capacity at maximum inspiration |
| HRQoL | Health-related quality of life |
| IB | Investigator's Brochure |
| IFN-γ | Interferon-gamma |
| ILD | Interstitial lung disease |
| IND | Investigational New Drug Application |
| IPF | Idiopathic pulmonary fibrosis |
| IRB | Investigational Review Board |
| JC | Polyomavirus JC |
| LCQ | Leicester Cough Questionnaire |
| LFTs | Liver function test |
| MCP-1 | Macrophage chemotactic protein-1 |
| MCTM | Markov Chain Transition Matrix |
| mITT | Modified intention to treat |
| MPA | Mycophenolic acid |
| MPAG | phenolic glucuronide metabolite of MPA |
| MMF | Mycophenolate mofetil; same as CellCept |
| MMP | Matrix metalloproteinase |
| MOP | Manual of Procedures |
| mRSS | Modified Rodnan Skin Score |
| NIH | National Institutes of Health |
| NSIP | Non-specific interstitial pneumonia |
| OHRP | Office for Human Research Protections |
| PAH | Pulmonary arterial hypertension |
| PDGF | Platelet derived growth factor |
| PFD | Pirfenidone; same as Esbriet |
| PFT | Pulmonary function test |
| PI | Principal Investigator |
| Plac | Placebo |
| PML | Progressive multifocal leukoencephalopathy associated with JC virus |
| PP | Per protocol |
| PPI | Proton pump inhibitors |
| PRCA | Pure Red Cell Aplasia |
| PRO | Patient Reported Outcome |
| PROMIS-29 | Patient-reported outcomes measurement information system 29-item health profile |
| PVAN | Polyomavirus associated nephropathy |
| QA | Quality Assurance |
| QC | Quality Control |

| | |
|---|---|
| QGG | Quantitative ground glass |
| QHC | Quantitative honeycomb change |
| QIA | Quantitative image analysis |
| QILD-LM | Quantitative interstitial lung disease score in the lobe of maximal involvement |
| QILD-WL | Quantitative interstitial lung disease score in the whole lung |
| QLF-LM | Quantitative lung fibrosis score in the lobe of maximal involvement |
| QLF-WL | Quantitative lung fibrosis score in the whole lung |
| SABER | Statistical Analysis of Biomedical and Educational Research Unit |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SGRQ | St. George's Respiratory Questionnaire |
| SHAQ | Scleroderma Health Assessment Questionnaire |
| SLS | Scleroderma Lung Study |
| SMC | Safety Monitoring Committee |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SSc | Scleroderma (same as Systemic Sclerosis) |
| SSc-lc | Scleroderma with limited cutaneous features |
| SSc-dc | Scleroderma with diffuse cutaneous features |
| SSc-ILD | Scleroderma-related interstitial lung disease |
| TDI | Transitional Mahler Modified Dyspnea Index |
| TEAE | Treatment-emergent adverse event |
| TGF-β1 | Transforming growth factor beta-1 |
| TID | Three times daily |
| UCLA SCTC GIT 2.0 | University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale |
| UIP | Usual interstitial pneumonia |
| ULN | Upper limit of normal |
| UP | Unanticipated Problem |
| US | United States |
| WBC | White blood cell |

## STATEMENT OF COMPLIANCE

This trial will be conducted with Good Clinical Practice (GCP) and in accordance with the Code of Federal Regulations on the Protection of Human Subjects (21 CFR Part 50). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the applicable Institutional Review Boards (IRBs), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

Michael D. Roth, M.D. (Print/Type Name)
Signed:

(Signature)

Date: 11/17/2021 (version 2.5)

## PROTOCOL SUMMARY

| | |
|---|---|
| **Title:** | SCLERODERMA LUNG STUDY III (SLS III) |
| **Précis:** | A Phase II multi-center, double-blind, parallel group, randomized and placebo-controlled clinical trial addressing the treatment of patients with active and symptomatic Scleroderma-related interstitial lung disease (SSc-ILD). 150 patients who are either treatment naïve or only recently started treatment (≤6 mo of prior treatment with a potentially disease-modifying therapy) will be randomized in a 1:1 assignment to receive either oral mycophenolate mofetil (MMF) and a placebo (Plac) or a combination of oral MMF and oral pirfenidone (PFD), with both regimens administered for 18 months. The primary assessment will be the change from baseline over the 18 month treatment period, as measured at 3-month intervals, in the course of the Forced Vital Capacity measured as a percentage of the age-, height-, gender- and race-adjusted predicted value (FVC-%). Key secondary outcomes will include changes over time in dyspnea, skin score, diffusing capacity and high resolution computerized tomography (HRCT) measures of interstitial lung disease ILD). Tolerability and toxicity of the two treatments will also be assessed. |
| **Objectives:** | **Primary Hypothesis:**<br>The primary hypothesis is that the rapid onset and anti-fibrotic effects of PFD, which have been observed in the treatment of Idiopathic Pulmonary Fibrosis (IPF), will complement the delayed anti-inflammatory and immunosuppressive effects of MMF, to produce a significantly more rapid and/or greater improvement in lung function over time than occurs in patients receiving control therapy with MMF and Plac.<br><br>A secondary objective is to demonstrate that combination therapy with PFD and MMF is well tolerated, in comparison to MMF alone, and not associated with limiting toxicity that impacts on the overall treatment effect. |
| **Endpoints** | **Primary Endpoint:**<br>The primary endpoint is the change from baseline, measured at 3-month intervals, in the mean forced vital capacity (represented as the percentage of the age-, height-, gender- and race-adjusted predicted value, i.e. FVC-%) over the course of the 18-month double-blind treatment period.<br><br>**Pre-specified Secondary Endpoints:**<br>1. The change from baseline to 18 months, measured at 3-month intervals, in the following disease measures:<br>• Single-breath diffusing capacity for carbon monoxide (DLCO), calculated as a percent of the age-, height-, gender-, race- and hemoglobin-adjusted predicted value (DLCOHb-%). |

| | |
|---|---|
| | • Modified Rodnan Skin Score (mRSS).<br>• Transitional Mahler Modified Dyspnea Index (TDI).<br>• Patient Reported Outcomes (PROs), which provide subjective measures of dyspnea and quality of life based on patient responses to standardized patient questionnaires.<br>2. The change from baseline to 18 months in HRCT measures of SSc-ILD:<br>• Quantitative lung fibrosis score in the whole lung (QLF-WL).<br>• Quantitative lung fibrosis score in the lobe of maximal involvement (QLF-LM).<br>• Quantitative interstitial lung disease score in the whole lung (QILD-WL).<br>• Quantitative interstitial lung disease score in the lobe of maximal involvement (QILD-LM).<br>• Total lung capacity at maximum inspiration (HRCT-TLC)<br>3. Differences in the frequency distribution of individual patient responses when grouped into defined intervals of improvement or worsening (defined by the change in an outcome measure from baseline to 18 months) for the following outcome measures:<br>• Forced vital capacity (represented as the percentage of the age-, height-, gender- and race-adjusted predicted value, i.e. FVC-%)<br>• Single-breath diffusing capacity for carbon monoxide (DLCO), calculated as a percent of the age, height, gender and hemoglobin adjusted predicted value (DLCOHb-%).<br>• Modified Rodnan Skin Score (mRSS).<br>• Transitional Mahler Modified Dyspnea Index (TDI)<br>4. The time (in months) required for each treatment arm to achieve a 3.0% or greater improvement from baseline in the FVC-% over the 18-month treatment period.<br>5. A threshold analysis based on the percentage of subjects in each treatment arm achieving greater than a 5% improvement in FVC-% over the 18-month treatment period.<br>6. Tolerability and toxicity of MMF+Plac versus MMF+PFD over the course of 18 months. |
| **Population:** | 150 randomized participants from recruitment sites in the United States, including both male and female patients of an age $\geq$18 years, diagnosed with systemic scleroderma (SSc) as defined by the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria, who demonstrate evidence of active restrictive lung disease by pulmonary function testing, symptomatic dyspnea and any evidence of ground glass opacification (GGO) on baseline thoracic HRCT, and who meet the study definition of being either treatment naïve or recently started on treatment ($\leq$6 mo of prior treatment with a potentially disease-modifying therapy) and all other inclusion & exclusion criteria as detailed below. |

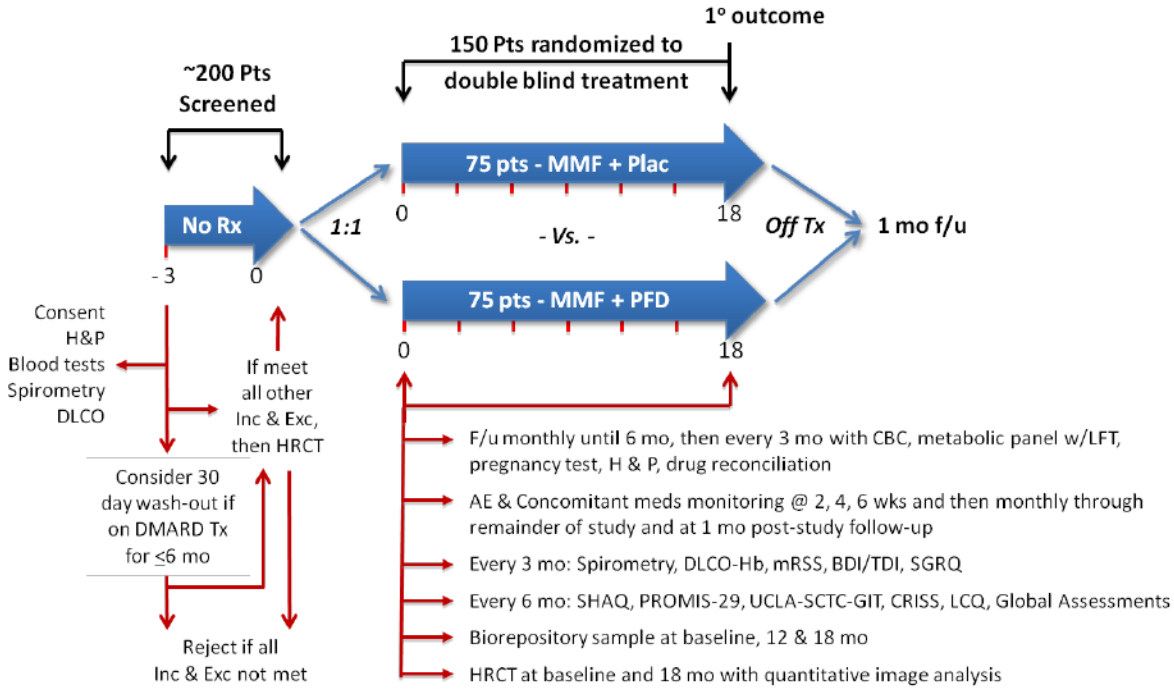
| | |
|---|---|
| **Phase:** | Phase II |
| **Number of Sites enrolling participants:** | Between 15 to 25 participating clinical sites<br>Please see Section 1, Key Roles, for a current list of participating sites |
| **Description of Study Agents:** | 1. Mycophenolate Mofetil (MMF)<br>Manufactured by: Teva Pharmaceuticals, Inc (Generic)<br>Oral Route<br>250 mg capsules<br>Target Dose:<br>1500 mg twice daily as tolerated with a 4-step titration at monthly intervals<br>a) 500 mg (two capsules) twice daily (BID) for 4 weeks<br>b) 1000 mg (four capsules) BID for 4 weeks<br>c) 1250 mg (five capsules) BID for 4 weeks<br>d) 1500 mg (six capsules) BID for remainder of study as tolerated.<br>2. Pirfenidone (PFD), same as Esbriet®<br>Manufactured by: Genentech, Inc.<br>Oral Route<br>267 mg capsules.<br>Target Dose:<br>801 mg three times daily as tolerated with a 3-step titration at 2 week intervals:<br>a) 267 mg (one capsule) three times daily (TID) for 2 weeks<br>b) 534 mg (two capsules) TID for 2 weeks<br>c) 801 mg (three capsules) TID for remainder of study as tolerated.<br>3. Placebo (Plac), matching to the PFD capsules<br>Manufactured by: Genentech, Inc.<br>Oral Route<br>267 mg capsules.<br>Target Dose:<br>801 mg three times daily as tolerated with a 3-step titration at 2 week intervals:<br>a) 267 mg (one capsule) three times daily (TID) for 2 weeks<br>b) 534 mg (two capsules) TID for 2 weeks<br>c) 801 mg (three capsules) TID for remainder of study as tolerated. |
| **Study Duration:** | Approximately 4 years total study duration, sub-divided into the following components:<br>a. 24 month enrollment period<br>b. 18-month randomized, double-blind treatment period per patient<br>c. 1 month follow-up period after completion of drug therapy<br>d. 6 month primary analysis period |
| **Participant Duration:** | 20-22 month subject participation period made up of the following components: |

| | |
|---|---|
| | - screening = 1-3 months<br>- randomized, double-blind treatment period = 18 months<br>- final follow-up period after completion of drug therapy = 1 month |
| **Inclusion Criteria:** | 1. Age ≥18 yrs<br>2. Scleroderma as determined by the 2013 ACR/EULAR classification criteria.<br>3. Grade ≥2 on the Magnitude of Task component of the Mahler Modified Dyspnea Index<br>(Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing less than three flights of stairs, or carrying a light load on the level.<br>4. FVC-% of ≤85% at screening.<br>5. Onset of the first non-Raynaud manifestation of SSc within the prior 84 months.<br>6. Presence of any GGO on thoracic HRCT<br>7. Repeat FVC-% at the baseline visit within 10% of the FVC-% value measured at screening. 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:** | 1. Disease features supporting the primary diagnosis of another connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus or mixed connective tissue disease (Features consistent with a secondary Sjogren syndrome or scleroderma-associated myopathy will be allowed).<br>2. FVC-% of <45% at either screening or baseline.<br>3. FEV1/FVC ratio <0.65 at either screening or baseline.<br>4. DLCOHb-% of <30% at screening ***or*** <25% at baseline.<br>a) All participants with a DLCOHb-% between 30 to 40% must have pulmonary artery pressures documented by either echocardiogram, right heart catheterization or magnetic resonance imaging in order to be considered for inclusion.<br>5. Diagnosis of clinically significant resting pulmonary hypertension requiring treatment or mild pulmonary hypertension requiring treatment with more than one oral medication as ascertained prior to study evaluation or as part of a standard of care clinical assessment performed outside of the study protocol.<br>6. Evidence of uncontrolled congestive heart failure, unstable ischemic heart disease, history of complicated pulmonary embolism impacting on heart or lung function, or unstable cardiac arrhythmia requiring chronic anticoagulation.<br>7. Clinically significant abnormalities on HRCT not attributable to SSc<br>8. Hematologic abnormality at screening including: |

| | |
|---|---|
| | a) Leukopenia (white blood cells [WBC] <4.0x$10^3$/µl)<br>b) Thrombocytopenia (platelet count <120.0x$10^3$/µl)<br>c) Clinically significant anemia [Hemoglobin (Hgb) <10.0 g/dl]<br><br>Participants with an identified and correctable etiology may be eligible if repeat testing within the maximal 90-day screening period meets all criteria.<br>9. A diagnosis of chronic liver disease or abnormal baseline liver function test (LFTs) or total bilirubin that are >2.0 x upper normal limit<br>10. Serum creatinine >2.0mg/dl<br>11. History of recurrent aspiration, uncontrolled heartburn, or gastroesophageal reflux disease (GERD) with a reflux scale score of >1.00 as determined by a UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Scale (UCLA SCTC GIT), Version 2.0.<br><br>Participants with uncontrolled heartburn or GERD that is amenable to medical management may be eligible if repeat testing within the maximal 90-day screening period meets this criteria.<br>12. Known achalasia, esophageal stricture or esophageal dysfunction sufficient to limit the ability to swallow medication.<br>13. Pregnancy (documented by serum pregnancy test) and/or breast feeding<br>14. If of child bearing potential (a female participant < 55 years of age who has not been postmenopausal for ≥ 5 years or who has not had a bilateral salpingectomy, 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, unless the participant chooses abstinence (to avoid heterosexual intercourse completely.) If a subject chooses abstinence, then a second reliable means of contraception is not needed.<br>15. Prior use of potential disease modifying antirheumatic drugs (DMARDs) according to the following exposure rules:<br>a) Use of oral cyclophosphamide (CYC), MMF, azathioprine or other oral or short half-life DMARDs (as detailed in Section 7.5.1a) for more than 6 months in the past year as determined at the time of the initial screening visit.<br>b) Treatment with more than three intravenous doses of CYC, one treatment course of Rituximab or other intravenous or injectable DMARDs (as detailed in Section 7.5.1b) in the past year.<br>c) More distant h/o treatment with a DMARD is allowed as long as the patient has a new diagnosis/new episode of active SSc-ILD since stopping that treatment and meets the criteria noted in 15a or 15b.<br>16. Use of CYC, MMF, azathioprine, Rituximab or other DMARD (as detailed in Section 7.5.1a&b) in the 30 days prior to the baseline visit |

| | |
|---|---|
| | unless the patient is on MMF and the responsible physician indicates that continued use is in the best clinical interest of the patient.<br>17. Active infection (lung, ulcers or elsewhere) whose management would be compromised by immunosuppression.<br>18. Other serious concomitant medical illness (e.g., active malignancy within the past 5 years other than surgically-removed local skin cancer such as a basal cell carcinoma), chronic debilitating illness (other than SSc), unreliability or drug abuse that might compromise the patient's participation in the trial.<br>19. Current use, or use within the 30 days prior to their baseline visit, of prednisone (or equivalent) in doses >10 mg/day.<br>20. Smoking of cigars, pipes, or cigarettes during the past 6 months.<br>21. Use of contraindicated medications, including medications with putative disease-modifying properties that do not meet the exposure limits described in Exclusion Criteria #15 and #16, moderate or strong inhibitors of cytochrome P450 (CYP) isozyme 1A2 (CYP1A2) (note ciprofloxacin allowed up to a dose of 500 mg twice daily), and moderate inducers of CYP1A2 (such as tobacco smoke, or phenytoin). See Section 7.5 for complete list. |

## SUMMARY SCHEMATIC OF STUDY DESIGN



## SUMMARY TABLE OF STUDY VISITS AND ASSESSMENTS**

| | Screen | | Randomized Double-blind Phase | | | | | | | | | | | | | | | | | | | | Exit visit* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **S1** | **S2** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** | **V10** | **V11** | **V12** | **V13** | **V14** | **V15** | **V16** | **V17** | **V18** | **V19** | **V20** | **V21** | **V22** |
| **Month on Study (Month = 28 days)** | Sc-1 | Sc-2 | 0 | 0.5 (14 days) ±7d | 1 (28 days) ±7d | 1.5 (42 days) ±7d | 2 (56 days) ±10d | 3 (84 days) ±10d | 4 (112 days) ±10d | 5 (140 days) ±10d | 6 (168 days) ±10d | 7 (196 days) ±10d | 8 (224 days) ±10d | 9 (252 days) ±10d | 10 (280 days) ±10d | 11 (308 days) ±10d | 12 (336 days) ±14d | 13 (364 days) ±10d | 14 (392 days) ±10d | 15 (420 days) ±14d | 16 (448 days) ±10d | 17 (476 days) ±10d | 18 (504 days) ±14d | Month 19 (532 days) ±10d |
| **Phone contact** | | | | X | | X | | | | | | X | X | | X | X | | X | X | | X | X | | X |
| **On-Site Visit** | X | X | X | | X | | X | X | X | X | X | | | X | | | X | | | X | | | X | |
| Complete H&P | X | | | | | | | | | | | | | | | | X | | | | | | | |
| F/u SSc-H&P | | | X | | X | | X | X | X | X | X | | | X | | | | | | X | | | X | |
| Vital signs | X | | X | | X | | X | X | X | X | X | | | X | | | X | | | X | | | X | |
| mRSS | | | X | | | | | X | | | X | | | X | | | X | | | X | | | X | |
| Study Consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Adverse events | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense meds | | | X | | X | | X | X | X | X | X | | | X | | | X | | | X | | | | |
| Drug reconciliation | | | X | | X | | X | X | X | X | X | | | X | | | X | | | X | | | X | |
| Mahler BDI/TDI | | | X | | | | | X | | | X | | | X | | | X | | | X | | | X | |
| SGRQ | | | X | | | | | X | | | X | | | X | | | X | | | X | | | X | |
| SHAQ, PROMIS-29, UCLA SCTC GIT, CRISS, LCQ, Global Assessments | UCLA SCTC GIT | | X (except CRISS) | | | | | | | | X | | | | | | X | | | | | | X | |
| **LABS:** | | | | | | | | | | | | | | | | | | | | | | | | |
| - CBC, diff, plat | X | | | | X | | X | X | X | X | X | | | X | | | X | | | X | | | X | |
| - Metabolic/liver | X | | | | X | | X | X | X | X | X | | | X | | | X | | | X | | | X | |
| - Serum Preg+ | X | | | | | | | | | | | | | | | | | | | | | | | |
| - Urine Preg+ | | | X | | X | | X | X | X | X | X | | | X | | | X | | | X | | | X | |
| HRCT | | X | | | | | | | | | | | | | | | | | | | | | X | |
| Spiro/DLCO | X | | X‡ | | | | | X | | | X | | | X | | | X | | | X | | | X | |
| Biorepository | | | X | | | | | | | | | | | | | | X | | | | | | X | |

‡Screen and Baseline FVC value must be within an absolute difference in percent-predicted of 10% - may repeat within 7 days if not and proceed to enroll if criteria met

+For women of childbearing potential, initial serum pregnancy testing will be carried out with subsequent urine testing at each visit using test kits provided by the study.

*Exit visit will also be carried out within 30 days (±10d) of early termination/withdrawal from the protocol. All subjects who terminate/withdraw early will be encouraged to return for the outcome assessments as detailed above for the 12 month (V15) and 18 month (V21) visits.

**Refer to Protocol Section 17.0 (EMERGENCY DISASTER/ PANDEMIC MANAGEMENT PLAN) for allowed adjustments in the event of a disaster/pandemic that disrupts patient or institutional access.

# 1 KEY ROLES

Study Roles and Participating Sites as of February 18, 2020

| | |
|---|---|
| **Administrative Coordinating Center**<br>**David Geffen School of Medicine at UCLA**<br>**Los Angeles, CA 90095-1690** | **Study Principal Investigator**<br>Michael D. Roth, M.D.<br>Professor, Pulmonary and Critical Care<br>Vice-Chair for Clinical Research Compliance<br>Department of Medicine, 43-229 CHS<br>David Geffen School of Medicine at UCLA<br>Los Angeles, CA 90095-1690<br>Tel: (310)206-7389; Fax: (310) 206-5088<br>*mroth@mednet.ucla.edu* |
| | **Director, HRCT Quantitative Image Analysis (QIA) Core**<br>Jonathan G. Goldin, M.D., Ph.D.<br>Professor of Radiology & Biomedical Physics Program<br>Executive Chief of Clinical Care, Dept. of Radiology<br>David Geffen School of Medicine at UCLA<br>Los Angeles, CA 90095-1690<br>Tel: (424) 259-8719; Fax: (424) 259-6521<br>*jgoldin@mednet.ucla.edu* |
| | **Director, UCLA Research Pharmacy Core**<br>Christina S. Shin, Pharm.D.<br>Investigational Drug Pharmacist<br>Investigational Drug Section<br>Ronald Reagan-UCLA Medical Center Pharmaceutical Services<br>757 Westwood Plaza Room, Room# B-504G<br>Tel: (310) 267-8522; Fax: (310) 267-3652<br>*csshin@mednet.ucla.edu* |
| | **Director, UCLA Pulmonary Function Quality Assurance Core**<br>Eric Kleerup, M.D.<br>Clinical Professor of Pulmonary & Critical Care<br>Department of Medicine, 37-131 CHS<br>David Geffen School of Medicine at UCLA<br>Los Angeles, CA 90095-1690<br>Tel: (310) 794-6593<br>*ekleerup@mednet.ucla.edu* |
| **Data Coordinating Center**<br>**University of Michigan**<br>**Ann Arbor, MI 48109-2029** | **Principal Statistician & Director of Data Coordinating Center**<br>Cathie Spino, D.Sc.<br>Associate Research Professor of Biostatistics<br>Director, Statistical Analysis of Biomedical<br>and Educational Research (SABER) Unit<br>School of Public Health<br>University of Michigan<br>1415 Washington Heights, Rm M4507<br>Ann Arbor, MI 48109-2029<br>Tel: (734) 615-5469; Fax: (734) 647-3711 |

| | | |
|---|---|---|
| | | *spino@med.umich.edu* |
| | | **Co-Principal Investigator**<br>Dinesh Khanna, MD, MSc<br>Division of Rheumatology<br>University of Michigan School of Medicine<br>300 North Ingalls Street, SPC 5422<br>Ann Arbor, MI 48109<br>Tel: (734) 232-2104; Fax: (734) 763-5761<br>*khannad@med.umich.edu* |
| **17 Participating Clinical Sites** | **1.** | **Boston University, School of Medicine**<br>Marcin Trojanowski, MD<br>Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (617) 638-7460<br>*trojanma@bu.edu* |
| | **2.** | **David Geffen School of Medicine at UCLA**<br>S. Samuel Weigt, M.D.<br>Principal Investigator<br>Division of Pulmonary & Critical Care<br>Department of Medicine<br>Tel: (310) 794-1996<br>*sweigt@mednet.ucla.edu* |
| | **3.** | **Georgetown University School of Medicine**<br>Virginia Steen, M.D.<br>Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (202) 444-6210<br>*steenv@georgetown.edu* |
| | **4.** | **Harvard / Brigham and Women's Hospital**<br>Paul Dellaripa, M.D.<br>Principal Investigator<br>Division of Rheumatology, Immunology and AllergyDepartment of Medicine<br>Tel: (617) 732-5548<br>*pdellaripa@bwh.harvard.edu* |
| | **5.** | **Hospital for Special Surgery**<br>Jessica Gordon, M.D.<br>Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (212) 606-1351<br>*gordonJ@hss.edu* |
| | **6.** | **Johns Hopkins University School of Medicine**<br>Laura Hummers, M.D. |

| | | |
|---|---|---|
| | | Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (410) 550-6819<br>*lhummers@jhmi.edu* |
| | **7.** | **Medical University of South Carolina**<br>Richard Silver, M.D.<br>Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (843) 792-3484<br>*silverr@musc.edu* |
| | **8.** | **Northwestern University Feinberg School of Medicine**<br>Jane Dematte-D'Amico, M.D.<br>Principal Investigator<br>Division of Pulmonary & Critical Care<br>Department of Medicine<br>Tel: (312) 695-1879<br>*j-dematte@northwestern.edu* |
| | **9.** | **Rutgers Robert Wood Johnson Medical School**<br>Vivien Hsu, M.D.<br>Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (732) 418-8484<br>*hsuvm@rwjms.rutgers.edu* |
| | **10.** | ~~**University of California San Francisco**~~<br>~~Jeffrey Golden, M.D.~~<br>~~Principal Investigator~~<br>~~Division of Pulmonary & Critical Care~~<br>~~Department of Medicine~~<br>~~Tel: (415) 353-2935~~<br>~~*jeff.golden@ucsf.edu*~~ |
| | **11.** | **University of Colorado Denver**<br>Joyce S. Lee, M.D.<br>Principal Investigator<br>Division of Pulmonary Sciences and Critical Care<br>MedicineDepartment of Medicine<br>Tel: (855) 586 4824;<br>*joyce.lee@cuanschutz.edu* |
| | **12.** | **University of Michigan Medical School**<br>Vivek Nagaraja, MBBS<br>Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (734) 936-9539 |

| | | |
|---|---|---|
| | | *nagarajv@med.umich.edu* |
| | **13.** | ~~**University of Minnesota Medical School**~~<br>~~Hyun Kim, M.D.~~<br>~~Principal Investigator~~<br>~~Division of Pulmonary & Critical Care~~<br>~~Department of Medicine~~<br>~~Tel: (612) 626-6127~~<br>~~*kimxx015@umn.edu*~~ |
| | **14.** | **University of Pittsburgh**<br>Robyn T Domsic, M.D.<br>Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (412) 648-4814<br>*rtd4@pitt.edu* |
| | **15.** | **University of Texas Medical School at Houston**<br>Maureen Mayes, M.D.<br>Principal Investigator<br>Division of Rheumatology<br>Department of Medicine<br>Tel: (713) 500-6905<br>*Maureen.D.Mayes@uth.tmc.edu* |
| | **16.** | **University of Utah School of Medicine**<br>Mary Beth Scholand, M.D.<br>Principal Investigator<br>Division of Pulmonary & Critical Care<br>Department of Medicine<br>Tel: (801) 581-7806<br>*Scholand@genetics.utah.edu* |
| | **17.** | **University of Washington School of Medicine**<br>Ganesh Raghu, MD<br>Principal Investigator<br>Division of Pulmonary & Critical Care<br>Department of Medicine<br>Tel: (206) 598-6190<br>*graghu@uw.edu* |
| | **20.** | **University of Indiana Health**<br>Ryan Boente, MD<br>Principal Investigator<br>Division of Pulmonary & Critical Care<br>Department of Medicine<br>Tel: (317) 278-0064<br>*rboente@iu.edu* |

# 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 BACKGROUND INFORMATION

### 2.1.1 Prevalence & Course of SSC-ILD & the Need for New Treatments

Systemic scleroderma (Systemic Sclerosis, SSc) is an autoimmune rheumatologic disorder characterized by the overproduction of auto-antibodies, tissue inflammation with small vessel vasculopathy, activation of tissue fibroblasts, and the deposition of extracellular matrix within skin and other defined organ sites including the lungs (55). It falls within the Food and Drug Administration's (FDA) designation of a rare disease, with estimates of the prevalence in the United States ranging between 40,000 to 165,000 overall cases (3). Although relatively rare, its impact is magnified by the fact that it primarily affects patients at middle-age, produces debilitating morbidity that can involve many organ systems, and is associated with significant mortality. Ten-year survival rates have recently been estimated at 65-70% (48).

Of patients with SSc, up to 74% have some evidence of interstitial fibrosis at the time of autopsy (9) and progressive interstitial lung disease (ILD) occurs in approximately 40% of patients. SSc-related ILD (SSc-ILD) has emerged as a leading overall cause of disease-related deaths as summarized in a report by Nikpour and Baran (**Table 2.1.1a;** 38,54).

**Table 2.1.1a. Causes of death in SSc: results from the University of Pittsburgh SSc cohort (54) and the EUSTAR registry (48) as reproduced from the report by Nikpour & Baron, 2014 (38)**

| | EUSTAR registry primary causes of death n (%) | Pittsburgh cohort primary causes of death % | |
|---|---|---|---|
| | 2004–2008 ($n=234$)[b] | 1972–1976 ($n=42$)[c] | 1997–2001 ($n=314$)[d] |
| SSc-related | 128 (55%) | 70% | 50% |
| Pulmonary | 78 (33%) | 19% | 36% |
| ILD | 45 (19%) | 4% | 22% |
| PAH | 33 (14%) | 15% | 14% |
| Myocardial | 33 (14%) | 10% | 5% |
| Renal | 10 (4%) | 31% | 3% |
| Gastrointestinal | 7 (3%) | 12% | 4% |
| Multiorgan | – | – | 4% |
| Non-SSc related | 96 (41%) | 31% | 50% |
| Infection | 31 (13%) | 2% | 5% |
| Malignancy | 30 (13%) | 10% | 7% |
| Cardiovascular | 28 (12%) | 3% | 2% |
| Other | 7 (3%) | 7% | 1% |
| Unknown | 10 (4%) | 9% | 10% (13% 'pending'[a]) |

ILD, interstitial lung disease; PAH, pulmonary arterial hypertension, SSc, systemic sclerosis
[a]Cause of death not assigned at the time of publication
[b]Among 5860 patients at risk; although there were 283 deaths, death questionnaires were completed in 234 patients for whom data are summarized in this table
[c]Among 221 patients at risk
[d]Among 1508 patients at risk

SSc-ILD usually emerges early during the inflammatory phase of the disease and rapidly transitions to the local deposition of collagen and destructive tissue changes (40,57). In fact, when the average annual decline in lung function was mapped out over time in a large cohort of 889 SSc patients, the

greatest decrease in lung function was found to occur early, within the first few years after diagnosis, after which time further decline was rather limited (**Figure 2.1.1a/b**; 46). The median survival for patients with SSc-ILD is in the range of 5-8 years and the extent of pulmonary involvement has repeatedly been found to correlate in an independent manner as a risk factor predicting time to death (16,35,38,46-47).

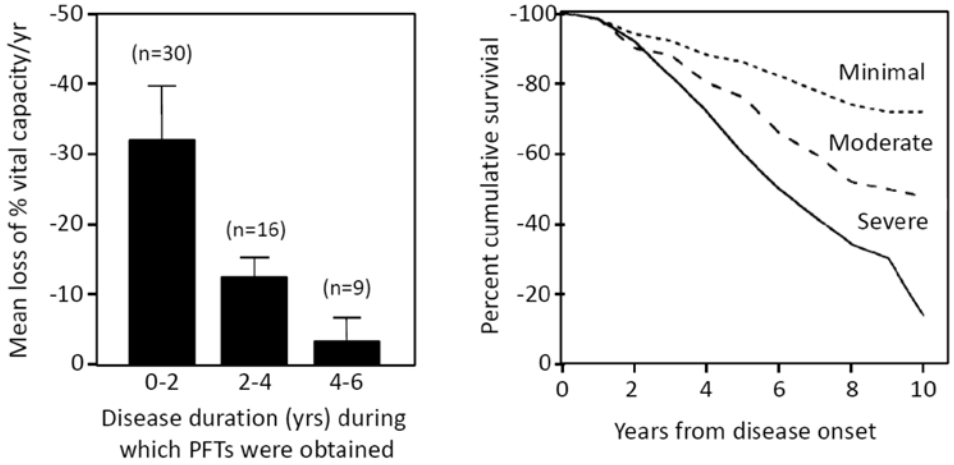



**Figure 2.1.1a (above, left).** Mean loss of percent vital capacity occurring over 2-year time periods in 55 patients whose initial pulmonary function tests (PFTs) were performed during the first 5 years of scleroderma symptoms. (*adapted from ref 46*).

**Figure 1b. (above, right)** Percent cumulative survival rate from onset of disease in patients grouped according to their lowest forced vital capacity. Those with severe restrictive lung disease had the worst prognosis ($p<0.01$). (*adapted from ref 46*).

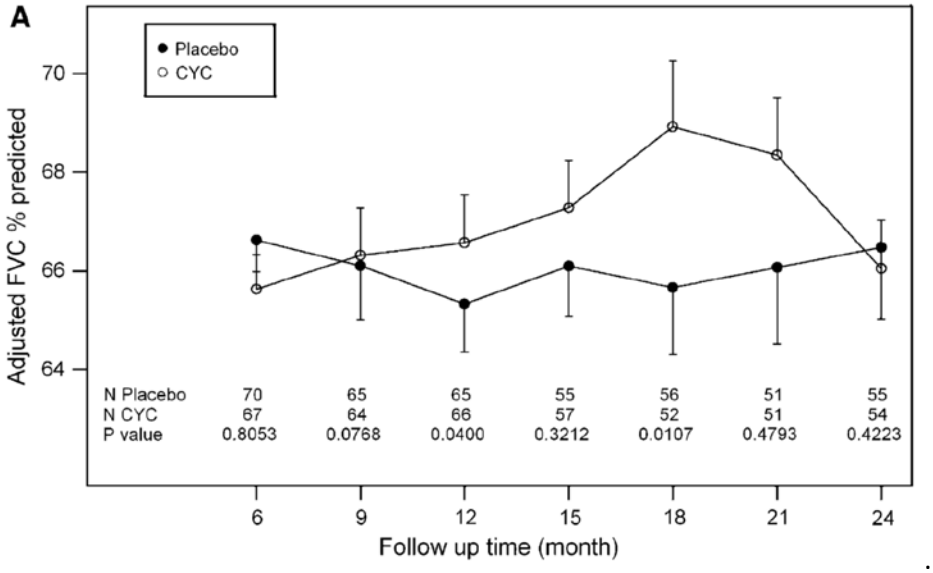
Based on such information, a strong argument can be made that the identification of SSc-ILD and targeted early interventions that reduce or reverse the impact of lung inflammatory and fibrosis have the potential to significantly reduce patient morbidity and mortality.

### 2.1.2 Effectiveness of Immune Suppression for the Treatment of SSc-ILD

SSc-ILD is characterized by a combination of interstitial and alveolar inflammation, vascular injury with endothelial activation/apoptosis, and evidence of activation of fibroblasts and pro-fibrotic signaling cascades (56). Based on the proposed linkage between inflammation and fibrosis, immunosuppression was initially investigated as the treatment of choice in Scleroderma Lung Study I (SLS I; 51). One-hundred fifty-eight (158) patients with SSc-ILD were randomized into a placebo-controlled double-blind trial to evaluate a 1-year treatment with oral cyclophosphamide (CYC) on the course of forced vital capacity as a percentage of the age-, height-, gender- and race-adjusted predicted value (FVC-%) and several secondary outcomes. There was a modest but statistically-significant difference between the treatment arms at the 12-month primary outcome (51) which continued to increase over time until a maximal treatment effect was observed at 18 months; 6 months after stopping immunosuppressive therapy (50, **Figure 2.1.2a**). At this point, using a longitudinal statistical model and a modified intention to treat (m-ITT) approach to take into account all available data, the average improvement in absolute FVC-% was 2.67% comparing the lung function in the active treatment arm to that in the placebo (Plac) group ($p=0.0107$). SLS I was the first randomized controlled trial to demonstrate that SSc-ILD responds to immunosuppression with placebo-adjusted improvements in pulmonary function as well as associated improvements in

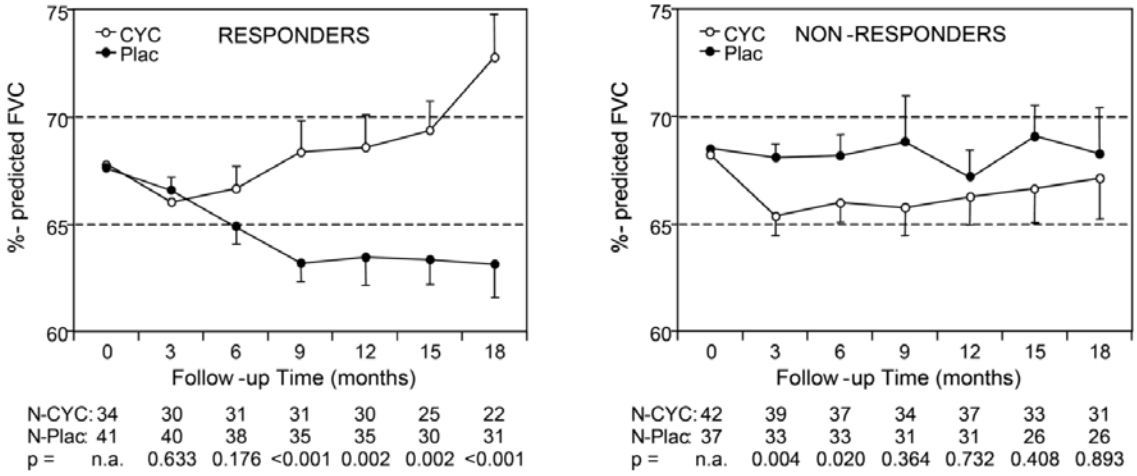
the patient's perception of dyspnea, objective measurements of skin disease, and health-related quality of life (HRQoL) when compared to an untreated control arm (26,50-51).

**Figure 2.1.2a (below).** Time course from 6 to 24 months of mean values (±SE) for the FVC-% of participants in the Plac and CYC treatment groups of the SLS I study determined using a longitudinal model that adjusted for baseline % predicted values, maximal high-resolution computed tomography–scored fibrosis, and non-ignorable missing data. Numbers of patients in each treatment group at each visit are shown, along with the P values for the between-treatment differences obtained from Huber's robust regression analysis with multiple imputation




Similar results were observed with the use of intravenous CYC in the Fibrosing Alveolitis in Scleroderma Trial (FAST study) carried out in the United Kingdom (19). While the overall magnitude of the response to CYC has been considered modest in these studies, a subset analysis of the SLS I patients suggested that distinct subsets of "responders" and "non-responders" might be prospectively identified based on the extent of interstitial disease on chest high resolution computerized tomography (HRCT) imaging and/or the extent of skin disease (44). When results from SLS I were retrospectively stratified based on these criteria, the average treatment effect in the responder population was approximately a 5 point difference at 12 months and a 10 point difference at 18 months with respect to the FVC-% (**Figure 2.1.2b**). Approximately one-half of the overall treatment effect in this responder population could be attributed to the ongoing deterioration that occurs in subjects treated with placebo, while the other one-half of the treatment response appeared to represent a significant improvement over time in subjects who were on active CYC therapy. In contrast, subjects identified as non-responders by this approach remained relatively stable with little deterioration if on placebo and little, if any, benefit from CYC (**Figure 2.1.2c**).

**Figure 2.1.2b (left) and 2c (right).** Time-trend curves. The changes in FVC-% from baseline to 18 months (adjusted for baseline FVC-%) are plotted for the cyclophosphamide (CYC) and placebo (Plac) arms (mean +SEM). The number of subjects (N) at each time-point and the p-value comparing groups is presented. (A) There was a small but significant difference between the treatment arms at 18 months when results were plotted for all patients. (B) Dividing the study population into Responder and Non-responder subsets resulted in two distinct plots with a highly-significant treatment effect from 9 to 18 months occurring only in the Responder population.




In Scleroderma Lung Study II, a two year course of daily oral mycophenolate mofetil (MMF) was evaluated as an alternative to one year of daily oral CYC (followed by placebo in the second year). The goals were to evaluate whether MMF, an alternative immunosuppressant, would induce clinical responses, extend the duration of the treatment effect, and produce a longer lasting outcome with less toxicity (bone marrow suppression, hemorrhagic cystitis or malignancies) than CYC (14,42). The primary outcome from the SLS II trial confirmed that both MMF and CYC significantly improved lung function compared to that at baseline with no difference between the study arms (52, **Figure 2.1.2d/e**).

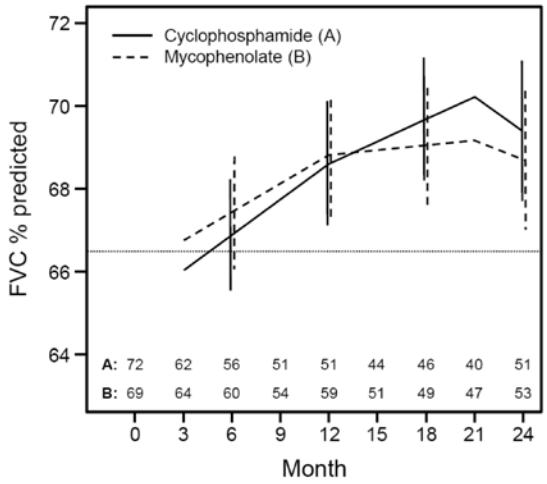



**Figure 2.1.2d (left).** Absolute change in FVC-% from baseline by treatment arm. Estimates of the absolute changes in mean FVC-% in the two treatment arms at three month intervals from baseline to 24 months were calculated using a pre-specified joint longitudinal model that linked a linear mixed-effects model with a cause-specific hazards model and took into account the time to cause-specific drop-out, treatment failure and/or death. 95% confidence intervals for the estimates are shown for the data at 6, 12, 18 and 24 months.

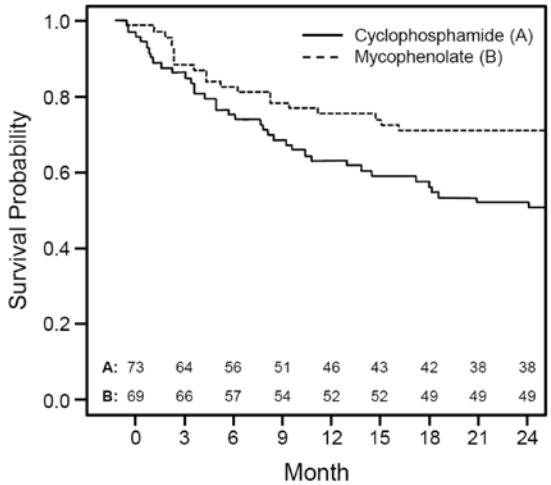


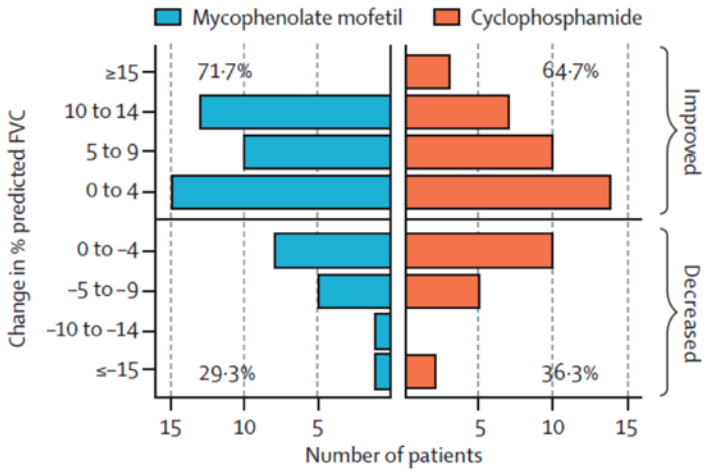

**Figure 2.1.2e (right).** A number of patients who received at least one dose of study medication prematurely withdrew or were withdrawn from study treatment at various times during the study due to adverse events, noncompliance, loss to follow-up or having met the protocol- definition of treatment failure. As an overall measure of tolerability, time to withdrawal from the study medication or treatment failure was significantly shorter in the CYC arm (p=0.019; log rank test) and consistent with the hypothesis that MMF is better tolerated and associated with less dose-

limiting toxicity.

As hypothesized, MMF was also better tolerated with respect to the time to treatment failure or drug discontinuation (p=0.019; log rant test; **Figure 2.1.2e**) and its use was associated with fewer episodes of protocol-defined levels of anemia (CYC = 26; MMF = 18), leukopenia (CYC = 51; MMF = 5), neutropenia (CYC = 7; MMF = 3) and thrombocytopenia (CYC = 7; MMF = 0).

In order to better understand the modeled outcomes, frequency distribution histograms were prepared from the un-modeled outcome data in which the subject-by-subject change in FVC-% from baseline to 24 months were plotted for the two treatment arms in increments of a 5% improvement or worsening from baseline (**Figure 2.1.2f**). Very similar to outcomes portrayed by the joint model, the overall change (±SE) in FVC-% averaged 3.0+1.2 for the CYC arm and 3.3+1.1 for the MMF arm. The majority of subjects in both arms had improving FVC-% values over time (64.7% for CYC, 71.7% for MMF) and no significant difference was identified between treatments (p=0.55; Fisher's exact test). Of the 34 patients in the CYC arm and the 38 patients in the MMF arm with a positive change over time, the average (±SE) improvement was a 7.1±0.7 and 7.5± 0.9 change in FVC-%, respectively. Of the 17 patients in the CYC arm and the 15 patients in the MMF arm whose FVC-% declined over 24 months, the average (±SE) decrement was a 6.0±1.6 and 6.4±1.6 change in FVC-%, respectively. We noted that the majority of subjects who experienced decrements in lung function belonged to the subset in either arm that had stopped drug treatment prematurely. Similar to the observations from the SLS I study, values for the mRSS decreased (i.e. improved) in 73.6 % of subjects on CYC and 71.7 % of subjects on MMF, with most of these improvements being by ≥5 units. Mahler's Transitional Dyspnea Index (TDI) values increased (i.e. improved) by at least 1 unit in 59 % of subjects on CYC and 47.5% % of subjects on MMF, with most of these improvements being by ≥3 units in both arms. In most cases these individual improvements exceeded the minimal clinically important changes that have been described for both of these endpoints (22,25,52).

**Figure 2.1.2f.** Raw unmodeled data from all subjects completing the 24 month evaluation, regardless of whether they stayed on drug therapy or withdrew prematurely from the treatment phase of the protocol, was used to construct a frequency distribution of changes from baseline in FVC-% at 24 months, by treatment arm.




The relatively equivalent efficacy and improved tolerability of MMF, as compared to CYC, make a strong clinical argument for its use as the preferred immunosuppressive medication for SSc-ILD (10,52).

### 2.1.3 The Importance of Addressing Fibrosis in Addition to Inflammation

In addition to confirming the important role of inflammation and auto-immunity in driving SSc-ILD, the Scleroderma Lung Study also identified the extent of fibrotic interstitial lung changes on baseline

HRCT, i.e. linear reticular markings, as an important predictor of progressive lung destruction and treatment-related improvement in SSc-ILD (44). The important role of lung fibrotic changes on disease progression and mortality has also been observed in a number or retrospective and longitudinal studies (35,58). These observations prompted us to examine HRCT-based evidence of disease progression in patients who participated in the SLS I study. Quantitative computer aided HRCT measurements of fibrosis, ground glass changes and honeycomb changes were compared at baseline to scans performed after 12 months in the patients assigned to the Plac Arm (**Figure 2.1.3a**; 28). By far, the most frequently observed transition from one type of lung involvement to another related to the development of fibrotic reticulation and honeycomb changes (cumulative probability 0.29) while the progression to a ground glass appearance, usually associated with worsening inflammation, was infrequent (cumulative probability 0.04).

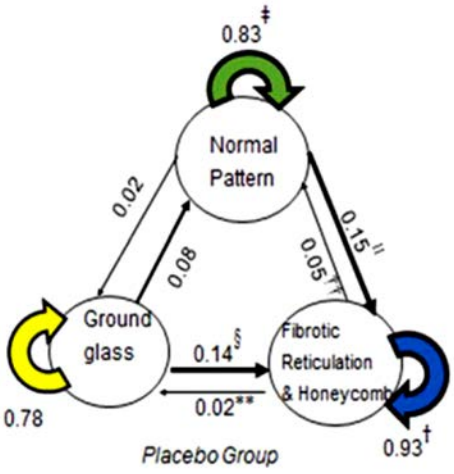



**Figure 2.1.3a.** A Markov Chain Transition Matrix (MCTM) was prepared for the patients participating in the Placebo Arm of the SLS I study based on quantitative computer aided image analysis of HRCT scans obtained on the same patients at baseline and again at 12 months. Means and standard deviations of the probability of transitioning from one pattern to another (straight arrows) or of remaining the same pattern (curved arrows near a circle) are shown for the most severe zone of disease involvement in each patient. Note that the most common transition from one type of disease finding to another related to the transition of both existing ground glass changes into fibrotic and honeycomb changes or the change from what appeared to be normal lung to fibrotic and honeycomb changes.

These observations further strengthen the linkage between fibrosis and progressive SSc-ILD. While SSc-ILD is most often thought of as a form of non-specific interstitial pneumonia (NSIP), differentiating it from the usual interstitial pneumonia (UIP) that occurs in Idiopathic Pulmonary Fibrosis (IPF), the work of Bouros et al. (6, **Table 2.1.3a/b**) makes a convincing argument that it is best characterized as fibrotic rather than cellular NSIP. In contrast to other rheumatologic diseases associated with ILD where cellular NSIP and lymphocytic infiltration appear to predominate, SSc-ILD demonstrates significant fibrosis combined with infiltration by neutrophils and eosinophils.

**Table 2.1.3a.** Histopathologic diagnosis, according to type of scleroderma and duration of exertional dyspnea. (*adapted from ref 6*)

| Histologic Subset | No. of Subjects | Type of Scleroderma (Limited/Diffuse) | Mean Duration of Dyspnea at Biopsy (*mo*) |
|---|---|---|---|
| NSIP | 62 (77.5%) | 43/19 | 11 |
| UIP | 6 (7.5%) | 4/2 | 28 |
| ESL | 6 (7.5%) | 5/1 | 24 |
| Miscellaneous* | 6 (7.5%) | 4/2 | 12 |

*Definition of abbreviations*: NSIP = nonspecific interstitial pneumonia; ESL = end-stage lung disease; UIP = usual interstitial pneumonia.

* Miscellaneous: respiratory bronchiolitis interstitial lung disease (n = 4), sarcoidosis (n = 1), organizing pneumonia (n = 1).

**Table 2.1.3b.** Bronchoalveolar lavage cell (BAL) differential (median, range) in usual interstitial pneumonia/end-stage lung disease, non-specific interstitial pneumonia, with data given separately for cellular and fibrotic non-specific interstitial pneumonia. (*adapted from ref 6*)

| | UIP/ESL | NSIP | Cellular NSIP | Fibrotic NSIP |
|---|---|---|---|---|
| Subjects, n | 10 | 57 | 12 | 45 |
| Alveolar macrophages | 82.5 | 78 | 76.5 | 79 |
| | 28–97 | 46–95 | 60–92 | 46–95 |
| Lymphocytes | 6 | 8 | 13.5 | 6 |
| | 1–22 | 0–45 | 6–30 | 0–45 |
| Neutrophils | 5 | 5 | 2.5 | 6 |
| | 1–55 | 1–41 | 1–12 | 1–41 |
| Eosinophils | 2.5 | 4 | 3 | 5 |
| | 0–4 | 0–19 | 0–10 | 0–19 |

*Definition of abbreviations*: ESL = end-stage lung disease; NSIP = Nonspecific interstitial pneumonia; OP = organizing pneumonia; RB-ILD = respiratory bronchiolitis interstitial lung disease; UIP = usual interstitial pneumonia.

In addition to this pathologic and CT evidence of fibrosis, there has been considerable effort at mapping the biologic environment associated with progressive SSc-ILD through the study of serum, plasma, peripheral blood, BAL fluid and lung tissue obtained from patients and in animal models. A number of these findings support the role of a pro-fibrotic environment. In some of the earliest studies, BAL obtained from the lungs of SSc-ILD patients were noted to have significantly higher levels of platelet derived growth factor (PDGF) and transforming growth factor beta-1 (TGF-β1) than BAL obtained from controls and these factors stimulated the proliferation of myofibroblasts (32). Baroni et al (4), identified autoantibodies from the serum of scleroderma patients that targeted and activated the PDGF receptor, resulting in collagen production and the generation of a myofibroblast phenotype. Thrombin levels are also increased in BAL fluid from patients with SSc-ILD and can induce profibrotic cytokines, growth factors, and extracellular matrix production associated with a myofibroblast phenotype, a key feature of fibrotic lung disease (1,14). Increased numbers of circulating fibrocytes – bone marrow-derived fibroblast precursors that have been reported in the circulation of patients with IPF, especially in the setting of acute exacerbation, are also observed in patients with SSc (4). Similarly, gene arrays and cytokine profiling have repeatedly identified the activation of related pro-fibrotic pathways in SSc-ILD patients including TGF-β1, collagens, interferon-gamma (IFN-γ) receptor, matrix metalloproteinase -7 (MMP-7), macrophage chemotactic protein-1 (MCP-1), and others as recently reviewed by Fan and associates (13).

Collectively, there is strong and clear evidence of the important role of pro-fibrotic signaling and active fibrosis in the pathogenesis of SSc-ILD.

### 2.1.4 Pirfenidone: a Drug of Interest for Treating the Fibrotic Aspect of SSc-ILD

PFD, currently marketed under the trade name Esbriet®, is an anti-inflammatory and anti-fibrotic drug that was approved by the FDA in 2014 for the treatment of IPF. PFD is a low molecular weight non-peptide molecule and biologically active when taken by the oral route (12). In vitro, PFD inhibits release of pro fibrotic factors by activated fibroblasts and macrophages while concurrently suppressing activation of pro-inflammatory factors. It reduces lung damage in animal models of pulmonary fibrosis and in human clinical trials it significantly reduces the rate of decline of lung function in patients with IPF (29,49).

Despite the success of cytotoxic therapy in resolving inflammation and preventing the progression of lung disease, it is not clear that this approach adequately addresses the considerable fibrosis that already exist in patients at the time of diagnosis or the fact that disease progression continues for several months after starting immunosuppression. As the majority of functional lung deterioration and fibrotic changes occur within the first few years of SSc-ILD, the delayed response to cytotoxic therapy is of particular concern.

In contrast to the slow onset of activity observed when CYC and MMF are used to treat SSc-ILD (50-52), PFD exhibits a relatively rapid onset of anti-fibrotic activity in patients with IPF (29). In IPF, the course of disease progression in patients on PFD and those on placebo begin to separate within the first few months and follow divergent trajectories over time (see **Figure 2.1.4a**).

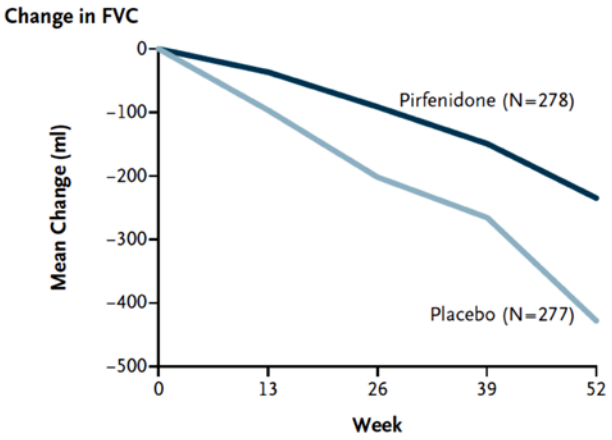



**Figure 2.1.4a: Time course of the response to PFD in patients with IPF.** The mean change from baseline in FVC (in ml) is plotted against time for the entire 52 weeks of therapy with PFD versus Plac. Using a ranked ANCOVA analysis, treatment with PFD resulted in a significant between-group difference in the primary end point, the change from baseline to week 52 in the percentage of the predicted FVC (P<0.001). The treatment effect was evident by week 13 and increased throughout the duration of the trial. The mean decline from baseline in FVC was 235 ml in the PFD group and 428 ml in the Plac group (absolute difference, 193 ml; relative difference, 45.1%; P<0.001). *(Adapted from ref# 29*)

This rapid effect, if it occurs in SSc-ILD, should complement the slower onset of action associated with cytotoxic therapy alone. As can be seen from SLS I data (see **Figures 2.1.2a-b**), patients on Plac show progressive deterioration over the first year and significant improvement from CYC was not observed until at least 6-9 months into therapy. A nearly identical pattern, with a delayed onset of the treatment effect, was observed with the use of MMF in SLS II (see **Figure 2.1.2d**). In addition, given its different mechanism of action, the hope is that PFD might produce at least additive effects with respect to the ultimate improvement in lung function. Preliminary toxicity and tolerability testing has already been carried out in patients with SSc-ILD (20) and suggest that PFD is reasonably tolerated when given alone and in patients who are on concurrent therapy with MMF. Given these differences in the rapidity of onset and mechanisms of action, we hypothesize that studies combining PFD and MMF should focus on outcome measures that address both the time to an observed improvement in lung function and the overall magnitude of the improvement.

### 2.1.5 The Documented Efficacy of Pirfenidone for the Treatment of IPF

Three randomized, double-blind, placebo-controlled Phase 3 studies evaluating PFD in patients with IPF have been conducted (PIPF-004, PIPF-006, and PIPF-016). A complete outcome summary detailing the findings from these studies is provided in the Esbriet Investigational Drug Brochure (11). The major findings are presented here as a brief summary.

#### 2.1.5.1 **Primary Study Endpoints in the treatment of IPF with PFD.**

In the pooled Phase 3 analysis (PIPF-004/006/016) of the primary endpoint, there was a clear effect of treatment with PFD in reducing the decline in percent predicted FVC compared with placebo ($p < 0.0001$, ANCOVA; **Figure 2.1.5a**, *adapted from ref #11*, Investigational brochure).

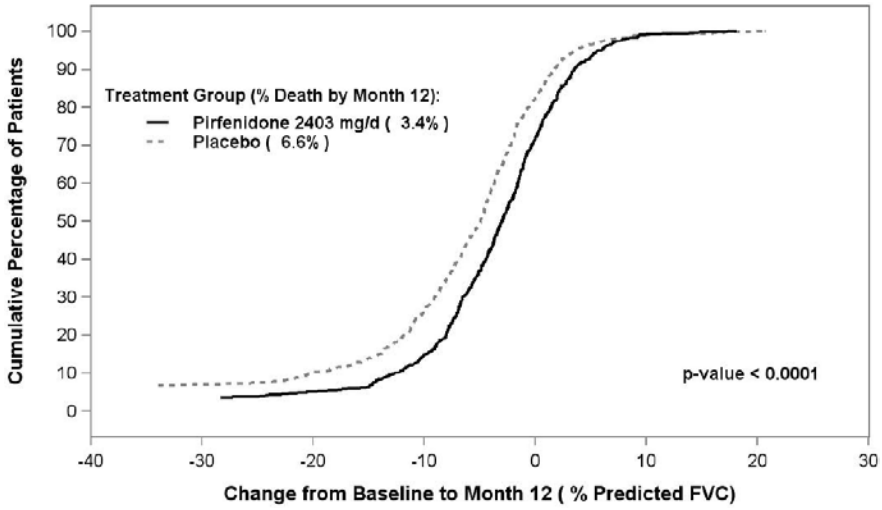



**Figure 2.1.5a Percent Predicted FVC:** Cumulative Distribution of Change from baseline to Month 12 in Pooled Phase 3 Studies (*adapted from ref #11*, Investigational Brochure)

There was a relative reduction of 43.8% in the proportion of patients with decline in percent predicted FVC $\geq$ 10% or death from Baseline at Month 12 in the PFD group compared with the placebo group, as well as a 59.3% relative increase in the proportion with no decline in percent predicted FVC (**Figure 2.1.5b**).

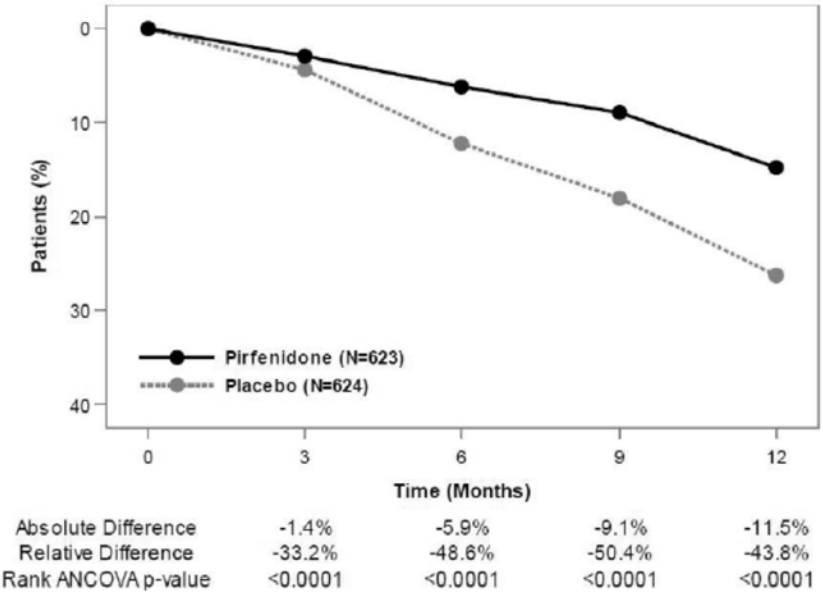



**Figure 2.1.5b Percent Predicted FVC:** Proportion of patients with decline of $\geq$ 10% to Month 12 in Pooled Phase 3 Studies

2.1.4.1 **Key Secondary Endpoints in the treatment of IPF with PFD.**

In the pooled Phase 3 analysis (PIPF-004/006/016) of key secondary endpoints, a beneficial effect of PFD on exercise tolerance was seen, represented by a statistically significantly lower decline from Baseline to Month 12 in the 6-minute walk test (6MWT) distance in the pirfenidone group compared with the placebo group (p = 0.0004) (11). There was also a 38% relative reduction in the risk of disease progression or death at Month 12 in pirfenidone-treated patients compared with placebo-treated patients (hazard ratio [HR] 0.62; 95% CI, 0.51 - 0.75; p < 0.0001) (11). In the mortality analysis, a 48% relative reduction in the risk of death from any cause favoring PFD was seen (HR 0.52; 95% CI, 0.31 -0.87; p =0.0107, log-rank test) (11). A smaller proportion of PFD-treated patients died compared with placebo-treated patients (3.5% vs. 6.7%, respectively) (11).

### 2.1.6 The Feasibility of Combining PFD with MMF for the Treatment of SSc-ILD

Directly relevant to this proposal, patients with SSc-ILD were randomized 1:1 in an initial safety and tolerability trial in patients with SSc-ILD (LOTUSS study, 20) to receive PFD when titrated from starting to final dose over a 2 week interval (one arm) vs a 4 week interval (second arm). Titration started at a dose of 801 mg/day and increased up to a maintenance dose of 2403 mg/day. Patients received PFD for 16 weeks in total and both treatment naïve patients and those already on other therapies, including treatment with MMF or CYC, were included in a stratified design. This design allowed an evaluation of whether the titration interval resulted in a difference in safety and tolerability and whether or not there were obvious differences when administered to treatment naïve patients or as an add-on therapy in combination with some form of immunosuppressive therapy. This trial Assessments included treatment-emergent AEs (TEAEs) and exploratory disease outcomes. Sixty-three patients were randomized; 96.8% experienced a TEAE and more patients reported TEAEs during the titration *vs* maintenance period consistent with the known pattern of TEAEs described when PFD has been used for the treatment of IPF. The most commonly reported TEAEs were also consistent with those observed for PFD when used in the treatment of IPF (nausea, headache, fatigue) and the frequency and type of TEAEs were similar regardless of titration schedule (**Table 2.1.6a**).

**Table 2.1.6a. Summary of TEAEs in the LOTUSS Study.**

| | Pirfenidone 2403 mg/day, number of patients (%) | | |
|---|---|---|---|
| TEAE[a] | 2-week titration group (*N* = 32) | 4-week titration group (*N* = 31) | Total (*N* = 63) |
| At least one TEAE | 31 (96.9) | 30 (96.8) | 61 (96.8) |
| Maximal intensity of TEAE[b] | | | |
| Mild | 7 (21.9) | 12 (38.7) | 19 (30.2) |
| Moderate | 15 (46.9) | 15 (48.4) | 30 (47.6) |
| Severe | 9 (28.1) | 3 (9.7) | 12 (19.0) |
| Life-threatening | 0 | 0 | 0 |
| Relationship of TEAE to study treatment[c,d] | | | |
| Not related | 3 (9.4) | 2 (6.5) | 5 (7.9) |
| Possibly related | 7 (21.9) | 6 (19.4) | 13 (20.6) |
| Related | 21 (65.6) | 22 (71.0) | 43 (68.3) |
| At least one TE SAE | 3 (9.4) | 0 | 3 (4.8) |
| At least one treatment-related TE SAE | 1 (3.1) | 0 | 1 (1.6) |
| Discontinuation of study treatment due to TEAE | 5 (15.6) | 1 (3.2) | 6 (9.5) |
| Death as an outcome of a TEAE | 0 | 0 | 0 |

| | Pirfenidone 2403 mg/day, number of patients (%) | | |
|---|---|---|---|
| | 2-week titration group (*N* = 32) | 4-week titration group (*N* = 31) | Total (*N* = 63) |
| **TEAEs reported in ≥10% of patients overall** | | | |
| Gastrointestinal disorders | 24 (75.0) | 25 (80.6) | 49 (77.8) |
| Nausea | 16 (50.0) | 15 (48.4) | 31 (49.2) |
| Diarrhea | 9 (28.1) | 10 (32.3) | 19 (30.2) |
| Vomiting | 9 (28.1) | 9 (29.0) | 18 (28.6) |
| GERD (including worsening GERD) | 6 (18.8) | 7 (22.6) | 13 (20.6) |
| Dyspepsia | 4 (12.5) | 4 (12.9) | 8 (12.7) |
| Constipation | 5 (15.6) | 2 (6.5) | 7 (11.1) |
| Stomach discomfort | 3 (9.4) | 4 (12.9) | 7 (11.1) |
| General disorders and administration-site conditions | 21 (65.6) | 15 (48.4) | 36 (57.1) |
| Fatigue | 13 (40.6) | 10 (32.3) | 23 (36.5) |
| Asthenia | 2 (6.3) | 5 (16.1) | 7 (11.1) |
| Metabolism and nutrition disorders | 6 (18.8) | 5 (16.1) | 11 (17.5) |
| Anorexia | 5 (15.6) | 2 (6.5) | 7 (11.1) |

However, more patients discontinued treatment due to TEAEs in the 2- *vs* 4-week titration group (5 *vs* 1, respectively); all discontinuation events occurred >3 weeks after reaching the full dose of pirfenidone. MMF, taken by 63.5% of patients in addition to PFD, did not appear to affect tolerability in the stratified analysis. Exploratory disease outcomes remained largely unchanged.

The tolerability profile of PFD in this preliminary study of SSc-ILD was therefore considered to be similar to that in IPF. Tolerability was not affected by titration length or concomitant MMF, although more subjects prematurely discontinued therapy in the 2 week titration as compared to the 4 week titration, leading to the hypothesis that tolerability might be improved when a slower titration is employed. The findings support the clinical feasibility of evaluating PFD when combined with MMF in future clinical trials in patients with SSc-ILD.

## 2.2 RATIONALE AND STUDY APPROACH

Scleroderma Lung Study III proposes to investigate a new combination therapy for patients with SSc-ILD that will combine the established effects of immunosuppression, as mediated by MMF, with the anti-fibrotic effects of PFD. The primary hypothesis is that the rapid onset and anti-fibrotic activity of PFD, which have been observed in the treatment of IPF, will complement the delayed anti-inflammatory and immunosuppressive effects of MMF, to produce a significantly more rapid and/or greater improvement in lung function over time than occurs in patients receiving control therapy with MMF (and Plac) alone. A secondary objective is to demonstrate that combination therapy with PFD and MMF is well tolerated, in comparison to MMF alone, and not associated with limiting toxicity that impacts on the overall treatment effect.

There are several important concepts that collectively provide a strong rationale for the proposed study:

**First**, SSc is a devastating disease in which pulmonary manifestations are the most frequent cause of morbidity and mortality (9,38,54). 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**, SSc-ILD is a rare condition with estimates of the prevalence in the United States ranging between 40,000 to 165,000 overall cases (3), and falls within the Food and Drug Administration's (FDA) designation of a "rare disease" for which there are limited FDA-approved therapies. Studies that focus on novel clinical approaches to treatment are considered a high priority.

**Third**, the SLS Investigators and the collaborative infrastructure that they have developed represent a well-established resource for carrying out clinical studies targeting the treatment of SSc-ILD. The identification and participation by centers of excellence in SSc-ILD, the collaborative interaction that occurs between pulmonologists and rheumatologists in the generation and conduct of the research, and the integration of key ancillary resources such as CT imaging and translational biology, all represent unique strengths of the SLS Investigators that are not likely to be reproduced elsewhere (10,26-27,50-52).

**Fourth**, while SLS I and II focused on establishing the benefits of cytotoxic therapy (utilizing CYC and/or MMF) for SSc-ILD, the improvements in lung function remain modest and it is reasonable to speculate that a combination therapy, which addresses perceived limitations in the use of cytotoxic therapy, might enhance the treatment effect to a level that is universally appreciated as efficacious.

**Fifth**, given that the predominant pathology in SSc-ILD is a fibrotic form of NSIP (6), the addition of an anti-fibrotic drug like PFD with proven efficacy in the treatment of IPF appears logical (2,29,36,39,43).

**Sixth**, as it can take up to 6 months of cytotoxic therapy before responses are apparent, during which time lung disease may progress (51-52), it is rational to add a drug like PFD that has a rapid onset of action that might ameliorate the ongoing decline in lung that occurs for months after starting MMF. This is particularly relevant when the most active decline in lung function is known to occur early in the course of the disease (46).

**Seventh**, given that MMF and PFD act by different mechanisms, it is reasonable to hypothesize that their combined use might produce additive or synergistic effects on lung function.

**Eighth**, as demonstrated in the LOTUSS study (20), it is expected that PFD is safe to administer to patients with SSc-ILD and can be used in conjunction with MMF with an acceptable tolerability and toxicity profile.

As a result of all of these considerations, we have designed SLS III as a two-arm Phase II clinical trial in which all patients will receive background therapy with MMF as the best tolerated cytotoxic therapy with documented clinical impact on the course of FVC-% over time (10,52). The inclusion and exclusion criteria, outcome measures, visit schedules and analysis approaches that have been developed and refined in the SLS I and SLS II studies will be carried forward, with only minor modification, and thereby provide a solid basis for the SLS III protocol. Treatment will last 18 months: the time associated with maximal response to cytotoxic therapy as defined in SLS I and II (10,50). In addition, patients will receive either PFD or matching Plac in a randomized double-blinded manner in order to objectively evaluate whether combination therapy produces a superior outcome when compared to cytotoxic therapy alone. The primary outcome will focus on the change from baseline in the mean forced vital capacity, measured as the percentage of the age-, height-, gender- and race-adjusted predicted value (FVC-%) over the course of the 18-month double-blind treatment period. FVC-% will be measured at baseline (pre-treatment) and then quarterly after treatment begins during the entire double-blind treatment period (i.e., months 3, 6, 9, 12, 15 and 18). A number of secondary outcomes are defined, following the logic and models developed in the SLS I and II studies. Given that the trajectories of the primary endpoint are expected to differ because of the mechanisms of action (and the time course of action) of the two treatment modalities, a longitudinal analysis approach incorporating all time points will be employed. Specifically, the endpoint will be analyzed using a linear mixed model with participant-month in the study (3, 6, 9, 12, 15 and 18) as the unit of analysis and the change from baseline in FVC-% as the outcome, with terms for treatment group, baseline FVC-%month and the interaction of treatment group with month used as fixed covariates. Study participant will be treated as a random effect to account for the correlation of outcomes over time within a participant. The model generates adjusted estimates of

change from baseline in the FVC-% for each treatment group and month, and an F-test will be used to test the hypothesis that the mean change from baseline during the treatment period differs between the two treatment groups.

## 2.3 POTENTIAL RISKS AND BENEFITS

### 2.3.1 Known Potential Risks

Two active drugs in oral capsule form will be administered to patients and include Mycophenolate Mofetil (MMF; Generic, Teva Pharmaceuticals, Inc.) and Pirfenidone (PFD; same as Esbriet®, Genentech, Inc.). They are both FDA approved medications for other related medical indications, but neither is currently approved by the FDA for use in the treatment of SSc-ILD. MMF is approved for use as an immunosuppressant in solid organ transplantation (cardiac, hepatic and renal) at doses up to 1.5 g twice daily and for the treatment of Lupus nephritis, an autoimmune manifestation of systemic lupus erythematosus, in the dose range of 1 to 3 g daily. PFD is currently approved for the treatment of IPF at a recommended dose of 801 mg (3 capsules of 267 mg each) 3 times daily. They will be administered in this study at doses that fall within these FDA-defined dosing ranges but as experimental therapy for SSc-ILD.

This section will summarize their known risks, when applicable, from the FDA-approved package inserts. In addition, details are provided regarding observed adverse events when used in clinical investigations that were closely related to those proposed by this protocol. Letters authorizing cross-filing to existing FDA data from a pharmaceutical manufacturer of these drugs is also provided in support of this protocol and the related IND filing. An inactive placebo capsule (Plac; matching to PFD, Genentech, Inc.) will also be administered to study participants but will not be considered further in this section.

#### 2.3.1.1 Mycophenolate Mofetil

2.3.1.1.1 **Black Box Warnings:**

a) ***Embryofetal Toxicity.*** Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning.
b) ***Malignancies And Serious Infections.*** Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe MMF. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

2.3.1.1.2 **Contraindications:**

Allergic reactions to MMF have been observed; therefore, MMF is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product.

2.3.1.1.3 **Warnings and Precautions:**

a) ***Embryofetal Toxicity.*** MMF can cause fetal harm when administered to a pregnant female. Use of MMF during pregnancy is associated with an increased risk of first

trimester pregnancy loss 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, kidney and nervous system.

b) ***Pregnancy Exposure Prevention and Planning.*** Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning.

c) ***Lymphoma and Malignancy.*** Patients receiving immunosuppressive regimens involving combinations of drugs, including MMF, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. 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 renal, cardiac, and hepatic transplant patients. In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed.

d) ***Serious Infections.*** Patients receiving immunosuppressants, including MMF, are at increased risk of developing bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

e) ***New or Reactivated Viral Infections.*** Polyomavirus associated nephropathy (PVAN), JC virus associated progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) infections, reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including MMF. Reduction in immunosuppression should be considered for patients who develop evidence of new or reactivated viral infections. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

   PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for PVAN.

   PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

   The risk of CMV viremia and CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease.

   Viral reactivation has been reported in patients infected with HBV or HCV. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

f) ***Neutropenia.*** Severe neutropenia [absolute neutrophil count (ANC) <0.5 x 103/µL] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving MMF 3 g daily (see ADVERSE REACTIONS). Patients receiving MMF should be monitored for neutropenia. The development of neutropenia may be related to MMF itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (ANC <1.3 x 103/µL), dosing with MMF should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. Neutropenia has been observed most frequently in the period from 31 to 180 days posttransplant in patients treated for prevention of renal, cardiac, and hepatic rejection. Patients receiving MMF should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

g) ***Pure Red Cell Aplasia (PRCA).*** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. The mechanism for MMF induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction orcessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

h) ***Gastrointestinal Disorders.*** Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with MMF 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal bleeding (requiring hospitalization) were observed. Gastrointestinal perforations have rarely been observed. Most patients receiving MMF were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with MMF. Because MMF has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, MMF should be administered with caution in patients with active serious digestive system disease.

i) ***Concomitant Medications.*** It is recommended that MMF not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically. In view of the significant reduction in the AUC of mycophenolic acid (MPA) by cholestyramine, caution should be used in the concomitant administration of MMF with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of MMF.

j) ***Patients with HGPRT Deficiency.*** MMF is an inosine monophosphate dehydrogenase inhibitor; therefore it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

k) ***Immunizations.*** During treatment with MMF, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective.

l) ***Drug Interactions.*** Drug interaction studies with MMF have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, sevelamer, trimethoprim/sulfamethoxazole, norfloxacin, and metronidazole. Drug interaction studies have not been conducted with other drugs that may be commonly

administered to renal, cardiac or hepatic transplant patients. MMF has not been administered concomitantly with azathioprine.

- Acyclovir. Coadministration of MMF (1 g) and acyclovir (800 mg) to 12 healthy volunteers resulted in no significant change in MPA AUC and Cmax. However, the phenolic glucuronide metabolite of MPA (MPAG) and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for MMF and acyclovir or its prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the concentrations of both drugs.
- Antacids With Magnesium and Aluminum Hydroxides. Absorption of a single dose of MMF (2 g) was decreased when administered to ten rheumatoid arthritis patients also taking Maalox® TC (10 mL qid). The Cmax and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when MMF was administered alone under fasting conditions. MMF may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that MMF and the antacid not be administered simultaneously.
- Proton Pump Inhibitors (PPIs). Coadministration of proton pump inhibitors (PPIs; e.g., lansoprazole, pantoprazole) in single doses to healthy volunteers and multiple doses to transplant patients receiving MMF has been reported to reduce the exposure to MPA. An approximate reduction of 30 to 70% in the Cmax and 25% to 35% in the AUC of MPA has been observed, possibly due to a decrease in MPA solubility at an increased gastric pH. The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and MMF. Because clinical relevance has not been established, PPIs should be used with caution when coadministered to transplant patients being treated with MMF.
- Cholestyramine. Following single-dose administration of 1.5 g MMF to 12 healthy volunteers pretreated with 4 g tid of cholestyramine for 4 days, MPA AUC decreased approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of MMF. Therefore, MMF is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.
- Cyclosporine. Cyclosporine (Sandimmune®) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10 stable renal transplant patients. The mean (±SD) AUC(0-12h) and Cmax of cyclosporine after 14 days of multiple doses of MMF were 3290 (±822) ng·h/mL and 753 (±161) ng/mL, respectively, compared to 3245 (±1088) ng·h/mL and 700 (±246) ng/mL, respectively, 1 week before administration of MMF. Cyclosporine A interferes with MPA enterohepatic recirculation. In renal transplant patients, mean MPA exposure (AUC0-12h) was approximately 30-50% greater when mycophenolate mofetil is administered without cyclosporine compared with when mycophenolate mofetil is coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine; changes in MPA exposure should be expected when switching patients from cyclosporine A to one of

the immunosuppressants which do not interfere with MPA's enterohepatic cycle (e.g., tacrolimus; belatacept).

- Telmisartan. Concommitant administration of telmisartan and MMF resulted in an approximately 30% decrease in MPA concentrations. Telmisartan changes MPA's elimination by enhancing peroxisome proliferator-activated receptor gamma expression, which in turn results in an enhanced UGT1A9 expression and activity.
- Ganciclovir. Following single-dose administration to 12 stable renal transplant patients, no pharmacokinetic interaction was observed between MMF (1.5 g) and intravenous ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and Cmax (n=10) were 54.3 (±19.0) μg·h/mL and 11.5 (±1.8) μg/mL, respectively, after coadministration of the two drugs, compared to 51.0 (±17.0) μg·h/mL and 10.6 (±2.0) μg/mL, respectively, after administration of intravenous ganciclovir alone. The mean (±SD) AUC and Cmax of MPA (n=12) after coadministration were 80.9 (±21.6) μg·h/mL and 27.8 (±13.9) μg/mL, respectively, compared to values of 80.3 (±16.4) μg·h/mL and 30.9 (±11.2) μg/mL, respectively, after administration of mycophenolate mofetil alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the two drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are coadministered, patients should be monitored carefully.
- Oral Contraceptives. A study of coadministration of MMF (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC(0-24h) was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC(0-24h) significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60% to 70%) in the data, especially for ethinylestradiol. Mean serum levels of LH, FSH and progesterone were not significantly affected. MMF may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. It is recommended to coadminister MMF with hormonal contraceptives (eg, birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used.
- Sevelamer. Concomitant administration of sevelamer and MMF in adult and pediatric patients decreased the mean MPA Cmax and AUC0-12h by 36% and 26% respectively. This data suggest that sevelamer and other calcium free phosphate binders should not be administered simultaneously with MMF. Alternatively, it is recommended that sevelamer and other calcium free phosphate binders preferentially could be given 2 hours after MMF intake to minimize the impact on the absorption of MPA.
- Trimethoprim/sulfamethoxazole. Following single-dose administration of MMF (1.5 g) to 12 healthy male volunteers on day 8 of a 10 day course of trimethoprim 160 mg/sulfamethoxazole 800 mg administered bid, no effect on the bioavailability of MPA was observed. The mean (±SD) AUC and Cmax of MPA after concomitant administration were 75.2 (±19.8) μg·h/mL and 34.0 (±6.6) μg/mL, respectively, compared to 79.2 (±27.9) μg·h/mL and 34.2 (±10.7) μg/mL, respectively, after administration of MMF alone.

- Norfloxacin and Metronidazole. Following single-dose administration of MMF (1 g) to 11 healthy volunteers on day 4 of a 5 day course of a combination of norfloxacin and metronidazole, the mean MPA AUC0-48h was significantly reduced by 33% compared to the administration of MMF alone ($p<0.05$). Therefore, MMF is not recommended to be given with the combination of norfloxacin and metronidazole. There was no significant effect on mean MPA AUC0-48h when MMF was concomitantly administered with norfloxacin or metronidazole separately. The mean (±SD) MPA AUC0-48h after coadministration of MMF with norfloxacin or metronidazole separately was 48.3 (±24) μg·h/mL and 42.7 (±23) μg·h/mL, respectively, compared with 56.2 (±24) μg·h/mL after administration of MMF alone.
- Ciprofloxacin and Amoxicillin plus Clavulanic Acid. A total of 64 MMF-treated renal transplant recipients received either oral ciprofloxacin 500 mg bid or amoxicillin plus clavulanic acid 375 mg tid for 7 or at least 14 days. Approximately 50% reductions in median trough MPA concentrations (predose) from baseline (MMF alone) were observed in 3 days following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA concentrations tended to diminish within 14 days of antibiotic therapy and ceased within 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction is an antibiotic-induced reduction in glucuronidase-possessing enteric organisms leading to a decrease in enterohepatic recirculation of MPA. The change in trough level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.
- Rifampin. In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure (AUC0-12h) has been observed with concomitant administration of MMF and rifampin. Therefore, MMF is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.
- Other Interactions. The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, coadministration of probenecid, a known inhibitor of tubular secretion, with MMF in monkeys results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion. Drugs that alter the gastrointestinal flora may interact with MMF by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

2.3.1.1.4 **Adverse Events:**

The principal adverse events reported during the administration of MMF include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections eg, opportunistic infection. Elderly patients (≥65 years), particularly those who are receiving MMF as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including CMV tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals.

Adverse event profiles reported in the packaging insert for MMF are those described for solid organ transplant recipients who were treated with MMF as one of many treatments administered following surgical organ transplantation. By definition, these patients had

recent major surgery, end-stage organ failure for one or more organ systems, variable degrees of recipient organ tissue type mismatch, and were receiving combination immunosuppression with one or more concurrent medications. The relevance of these reports to the administration of MMF to patients with autoimmune disease such as SSc, in the absence of organ system failure and concurrent immunosuppressive therapy, is unknown.

Information that is more relevant to the patient population and intended use described in this protocol comes from SLS II, where patients with SSc-ILD with similar characteristics were randomized to receive either oral CYC for one year followed by Plac for a second year (N=73) or a two year course of oral MMF (N=69). Adverse event data comparing these two study groups is summarized as follows:

a) ***Protocol defined and managed adverse events (AEs).*** According to the protocol, five specific types of adverse events were pre-defined as likely to be related to the administration of study drugs and to warrant protocol-defined management.
   - Anemia = Hgb <10.0 g/dl or <9.0 g/dl for those with Hgb <11.0 g/dl at enrollment
   - Leukopenia = WBC <2.5x$10^3$/µl
   - Neutropenia = neutrophil count <1.0x$10^3$/µl
   - Thrombocytopenia = Platelet count <100.0x$10^3$/µl
   - Hematuria = >25 Red blood cells (or 10-15 range on more than one routine urine analysis) in absence of a urinary tract infection or menses

These protocol-defined AEs were tracked and recorded for all subjects until the time they either completed the study or withdrew or were withdrawn from active participation. The development of protocol-defined AEs from the SLS II study are summarized below by treatment arm.

**Table 2.3.1.1.4a. Protocol-defined and managed adverse events reported for SLS II**

| | Mycophenolate mofetil | | Cyclophosphamide | |
|---|---|---|---|---|
| | Adverse events | Patients (n=69) | Adverse events | Patients (n=73) |
| **Adverse events*** | | | | |
| Leucopenia† | 5 | 4 (6%) | 51 | 30 (41%) |
| Neutropenia | 3 | 3 (4%) | 7 | 5 (7%) |
| Anaemia | 18 | 8 (12%) | 26 | 13 (18%) |
| Thrombocytopenia | 0 | 0 | 7 | 4 (6%) |
| Haematuria | 3 | 3 (4%) | 2 | 2 (3%) |

†p<0.05, Fisher's exact test comparing the number of patients experiencing AE
(some patients had more than one AE event).

The following conclusions were drawn from this data:

i. Anemia and Leukopenia were the dominant causes of protocol-defined AEs during treatment with MMF, accounting for 23/29 reported events.
ii. Absolute neutropenia, while a common occurance in patients receiving CYC, occured only rarely in those receiving MMF (4.3% of patients randomized to the MMF arm) and at rates reported when MMF is used for other indications.

iii. Thrombocytopenia, which occurs during the administration of CYC, was not observed in the MMF arm.

b) ***All adverse events by system or disease category.*** All AEs, categorized by system or disease category, were tracked and recorded for all study subjects until the time they either completed the study or withdrew or were withdrawn from active participation. Recorded AEs from the SLS II study are summarized below by treatment arm and according to the frequency of occurance (least to most frequent).

**Table 2.3.1.1.4b. All adverse events summarized by category and study arm**

| Category | Number of Reported AE | | | Number of Patients with AE | | |
|---|---|---|---|---|---|---|
| | Total | CYC | MMF | Total | CYC | MMF |
| | N | N (% of AE) | N (% of AE) | N | N (% of randomized) | N (% of randomized) |
| Cancer (including skin) | 6 | 2 (33.3) | 4 (66.7) | 6 | 2 (2.7) | 4 (5.8) |
| Immune System Disorders | 6 | 4 (66.7) | 2 (33.3) | 6 | 4 (5.5) | 2 (2.9) |
| Vision and Hearing | 10 | 8 (80.0) | 2 (20.0) | 8 | 6 (8.2) | 2 (2.9) |
| Hepatobiliary Disorders | 12 | 6 (50.0) | 6 (50.0) | 10 | 4 (5.5) | 6 (8.7) |
| Surgical & Medical Procedures | 17 | 6 (35.3) | 11 (64.7) | 11 | 5 (6.8) | 6 (8.7) |
| Psychiatric Disorders | 22 | 10 (45.5) | 12 (54.5) | 19 | 9 (12.3) | 10 (14.5) |
| Injury, Poisoning & Procedural Complications | 25 | 15 (60.0) | 10 (40.0) | 18 | 10 (13.7) | 8 (11.6) |
| Nervous System Disorders | 31 | 9 (29.0) | 22 (71.0) | 21 | 9 (12.3) | 12 (17.4) |
| Reproductive System & Breast Disorders | 36 | 17 (47.2) | 19 (52.8) | 27 | 12 (16.4) | 15 (21.7) |
| Metabolism & Nutrition Disorders* | 40 | 24 (60.0) | 16 (40.0) | 33 | 22 (30.1) | 11 (15.9) |
| Vascular Disorders | 66 | 33 (50.0) | 33 (50.0) | 41 | 22 (30.1) | 19 (27.5) |
| Cardiac Disorders | 67 | 32 (47.8) | 35 (52.2) | 39 | 21 (28.8) | 18 (26.1) |
| Renal & Urinary Disorders | 93 | 44 (47.3) | 49 (53.7) | 53 | 27 (37.0) | 26 (37.7) |
| General Disorders | 146 | 85 (58.2) | 61 (41.8) | 64 | 33 (45.2) | 31 (45.0) |
| Skin & Subcutaneous Tissue Disorders | 174 | 92 (52.9) | 82 (47.1) | 78 | 43 (58.9) | 35 (50.7) |

| Category | Number of Reported AE | | | Number of Patients with AE | | |
|---|---|---|---|---|---|---|
| | Total | CYC | MMF | Total | CYC | MMF |
| | N | N (% of AE) | N (% of AE) | N | N (% of randomized) | N (% of randomized) |
| Musculoskeletal & Connective Tissue Disorders | 181 | 102 (56.4) | 79 (43.6) | 68 | 34 (46.6) | 34 (49.3) |
| Blood & Lymphatic System Disorders* | 199 | 149 (74.9) | 50 (25.1) | 67 | 47 (64.4) | 20 (29.0) |
| Respiratory, Thoracic & Mediastinal Disorders | 223 | 102 (45.7) | 121 (54.3) | 91 | 45 (61.6) | 46 (66.7) |
| Gastrointestinal Disorders | 260 | 115 (44.2) | 145 (55.8) | 87 | 40 (54.8) | 47 (68.1) |
| Infections & Infestations | 290 | 139 (47.9) | 151 (52.1) | 109 | 57 (78.1) | 52 (75.4) |
| Total | 1904 | 994 (52.2) | 910 (47.8) | 139 | 71 | 68 |

*p<0.05, Fisher's exact test comparing the number of patients experiencing AEs.

The following conclusions were drawn from this data:

i. The distribution of AEs is similar to that observed in the SLS I study with the 5 most common AE categories including infections, GI disorders, respiratory and thoracic, blood and lymphatic, and musculoskeletal and connective tissue.
ii. While there were no significant differences between arms with respect to either the total # of AEs or the total # of patients with AEs, there was an unequal distribution between study arms with respect to two categories; blood and lymphatic disorders and metabolism and nutrition disorders. In each case, fewer events were observed in the patients treated with MMF as compared to those treated with CYC, supporting the overall conclusion from SLS II that treatment with oral MMF appears better tolerated than treatment with oral CYC.
iii. When broken down further, it was determined that the difference between groups for blood and lympatic disorders was primarily driven by significant differences in the number of patients experiencing leukocpenia and thrombocytopenia - reinforcing the findings from the recording of protocol-defined events noted above.
iv. When broken down further, no statistically significant difference between groups was identified for individual categories within the subset of metabolism and nutrition disorders. The only notable numerical imbalance (although not statistically significant) being for the category of weight loss, which occured more frequently in patients receiving CYC.

***c. Severe Adverse Events.*** All SAEs, categorized by system or disease category, were tracked and recorded for all study subjects. In addition, all SAE documentation was reviewed by an independent Morbidity and Mortality Committee composed of one rheumatologist, one pulmonologist and one general internal medicine specialist, who determined the relatedness of the SAE according to the study protocol (related to study

treatment, related to underlying disease, related to other causes or related to unknown causes).

**Table 2.3.1.1.4c-1. Serious adverse events reported for SLS II.**

| Category | # of Patients | # of SAEs | MMF | CYC |
|---|---|---|---|---|
| Cancer | 3 | 3 | 2 | 1 |
| Renal/Bladder | 2 | 2 | 1 | 1 |
| Syncope/ Seizures | 2 | 3 | 3 | 0 |
| Hematologic | 3 | 3 | 1 | 2 |
| Miscellaneous | 6 | 6 | 5 | 1 |
| Gastrointestinal | 6 | 7 | 2 | 5 |
| Musculoskeletal/ Skin | 6 | 7 | 4 | 3 |
| Respiratory Infection | 9 | 9 | 2 | 7 |
| Respiratory | 12 | 18 | 12 | 6 |
| Cardiac | 16 | 20 | 10 | 10 |
| **TOTAL** | **65** | **78** | **42** | **36** |

- Cancer cases included lymphoma and adenocarcinoma of the lung (2 cases)
- Renal/Bladder cases included one renal crisis with stroke and one bladder lesion with hematuria
- Hematologic cases included anemia (2 cases) and a blood clot (1 case)
- Miscellaneous cases included an assault, sulfa allergy, weight loss, and elective surgeries
- Gastrointestinal cases included dysphagia/vomiting, gastroenteritis, bile duct obstruction, and scleroderma bowel.
- Musculoskeletal/skin cases included arthritis, fractures, elbow pain/ulcer, and infected bursa with abscess
- Respiratory infections included influenza, bronchitis and pneumonia
- Respiratory cases included progressive dyspnea, respiratory failure, severe hypoxemia, progressive ILD, and shortness of breath
- Cardiac cases included heart failure, palpitations, arrhythmias, chest pain/pressure, pericarditis, cardiac cath, ischemic heart disease, and non-infective nodule on mitral valve

**Table 2.3.1.1.4c-2. Relatedness of Serious Adverse Events reported for SLS II.**

| | Mycophenolate mofetil | | Cyclophosphamide | |
|---|---|---|---|---|
| | Adverse events | Patients (n=69) | Adverse events | Patients (n=73) |
| **Serious adverse events‡** | | | | |
| Total | 42 | 27 (39%) | 36 | 22 (30%) |
| Related to treatment§ | 3 | 3 (4%) | 8 | 7 (10%) |
| Related to underlying disease§ | 16 | 9 (13%) | 16 | 13 (18%) |
| Due to other causes§¶ | 22 | 14 (20%) | 11 | 6 (8%) |
| Unknown cause§ | 3 | 3 (4%) | 3 | 3 (4%) |
| Death | .. | 5 (7%) | .. | 11 (15%) |

The following conclusions were drawn from this data:

i. SAEs occurred slightly more frequently in the MMF group than the CYC group (n=42 vs36), whereas numerically more SAEs in the CYC group (n=8) than in the

MMF group (n=3) were deemed by the Morbidity and Mortality Committee to be related to the study drug. No statistically significant differences were noted between treatment arms.

ii. Relatively equal numbers of serious adverse events were attributed to systemic sclerosis itself (16 in each group) or to other causes (MMF [n=11] vs CYC [n=14}.

iii. While a numerically greater number of Respiratory SAE's were observed in the MMF Arm (12) than the CYC Arm (6), only 4 were determined by the morbidity and mortality committee to be possibly or probably due to drug and three of these occurred in the CYC arm.

#### 2.3.1.2 Pirfenidone

2.3.1.2.1 **Black Box Warnings:**

None

2.3.1.2.2 **Contraindications:**

None

2.3.1.2.3 **Warnings:**

a) ***Elevated Liver Enzymes and drug-induced liver injury.*** Increases in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and bilirubin elevations have been reported in patients treated with PFD including cases of drug-induced liver injury. In postmarketing reporting, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome. Patients treated with PFD 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the PFD 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with PFD in all patients, then monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modifications or interruption may be necessary for liver enzyme elevations

b) ***Photosensitivity Reaction or Rash.*** Patients treated with PFD 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash.

c) ***Gastrointestinal Disorders.*** In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the PFD treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the PFD 2403 mg/day group

discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions.

2.3.1.2.4 **Adverse Events reported during the treatment of IPF:**

Adverse reactions related to Liver Enzyme Elevations, Photosensitivity Reaction or Rash, and Gastrointestinal Disorders represent the principal adverse reactions associated with the administration of PFD and have already been described in the Warnings section above and are detailed in the Investigational Brochure (11).

The safety of PFD has been evaluated in more than 1400 subjects with over 170 subjects exposed to PFD for more than 5 years in clinical trials. PFD was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of PFD and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to PFD was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on PFD compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the PFD than placebo treatment group are listed in **Table 2.3.1.2.4a** (*adapted from ref #12*).

**Table 2.3.1.2.4a.** Adverse reactions occurring in ≥10% of PFD (ESBRIET)-treated patients and more commonly than placebo in studies 1, 2, and 3 (*adapted from ref #12*).

| Adverse Reaction | % of Patients (0 to 118 Weeks) | |
|---|---|---|
| | ESBRIET 2403 mg/day (N = 623) | Placebo (N = 624) |
| Nausea | 36% | 16% |
| Rash | 30% | 10% |
| Abdominal Pain[1] | 24% | 15% |
| Upper Respiratory Tract Infection | 27% | 25% |
| Diarrhea | 26% | 20% |
| Fatigue | 26% | 19% |
| Headache | 22% | 19% |
| Dyspepsia | 19% | 7% |
| Dizziness | 18% | 11% |
| Vomiting | 13% | 6% |
| Anorexia | 13% | 5% |
| Gastro-esophageal Reflux Disease | 11% | 7% |
| Sinusitis | 11% | 10% |
| Insomnia | 10% | 7% |
| Weight Decreased | 10% | 5% |
| Arthralgia | 10% | 7% |

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of PFD-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during postapproval use of PFD. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

a) Blood and Lymphatic System Disorders: Agranulocytosis
b) Immune System Disorders: Angioedema
c) Hepatobiliary Disorders: Bilirubin increased in combination with increases of ALT and AST

2.3.1.2.5 **Adverse Events reported during the treatment of SSc-ILD:**

Directly relevant to this proposal, patients with SSc-ILD were treated in a multinational, open-label, randomized, parallel-group safety and tolerability trial (LOTUSS study; 11,20) and received PFD when titrated from starting to final dose over a 2 week interval (one arm) vs a 4 week interval (second arm). Titration started at a dose of 801 mg/day and increased up to a maintenance dose of 2403 mg/day. Patients received PFD for 16 weeks and the population included both treatment naïve patients and those already on other therapies, including treatment with MMF or CYC, in a stratified design. Most AEs were mild or moderate and resolved without sequelae; severe AEs were reported in 19%, most commonly fatigue, diarrhea, and nausea and consistent with the experience in IPF. Similarly, all of the most commonly reported (≥10%) AEs have been seen in pirfenidone IPF studies. The AE system organ class (SOC) with the greatest incidence was gastrointestinal disorders, with nausea, diarrhea, vomiting, GERD, dyspepsia, constipation, and stomach discomfort each occurring in ≥10% of patients. GI events were mostly mild or moderate and none led to study treatment discontinuation.

AEs of interest in this study (events known or suspected to be associated with PFD administration and occurring in organs or systems already affected in patients with scleroderma) were nausea (49.2%), vomiting (28.6%), and skin events: rash (20.6%), photosensitivity reaction (6.3%), erythema (4.8%), and follicular rash (1.6%). Almost all of these events were mild or moderate and considered related to study treatment. Three patients (4.8%) had SAEs (bronchitis, small intestinal obstruction, and pulmonary hypertension/interstitial lung disease [PAH/ILD]); all but the PAH/ILD events resolved. No deaths occurred during this study. There were no clinically relevant abnormal findings in clinical laboratory tests including liver function tests (LFT), vital signs, body weight, or ECGs.

### 2.3.1.3 Approaches to reduce risks associated with study drugs

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, while neither drug is approved for the treatment of SSc-ILD, they are approved for related conditions and will be used within the dosage range and with the accumulated knowledge of their effectiveness and potential toxicity gained from their prescribed uses. In addition, based on past experience with the administration of immunosuppressive therapies 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. The 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 leukoencephalopathy 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.

### 2.3.2 Known Potential Benefits

The two active drugs that will be employed to treat patients in this protocol, MMF and PFD, are both FDA approved treatments for medical conditions that are related to but not known to be the same as SSc-ILD. Neither is currently approved by the FDA for use in the treatment of SSc-ILD and therefore both are considered experimental in this respect. MMF is approved by the FDA for use as an immunosuppressant in solid organ transplantation and for the treatment of another type of autoimmune disease with end-organ dysfunction, Lupus nephritis. As presented in Section 2.1 on Background Information, the recent publication of primary outcome results from the SLS II study provides striking evidence that lung function, dyspnea and skin disease all improve over time in patients treated with MMF, which is in contrast to the known progression of disease that occurs without treatment (10,50-52), suggesting that it has a disease modifying effect and supporting its ongoing clinical evaluation as a potential treatment for SSc-ILD. PFD is currently approved for the treatment of IPF and as presented in Section 2.1 on Background Information, SSc-ILD shares some of the important features of IPF, providing a strong rationale for its evaluation as a potential therapy. However, at this point in time, there is no direct clinical evidence regarding the efficacy of PFD for the treatment of SSc-ILD.

# 3 STUDY OBJECTIVES AND PURPOSE

The primary purpose for this Phase II clinical investigation is to determine the relative efficacy and safety of combining two drugs with different mechanisms of action, PFD and MMF, for the treatment of Scleroderma-related ILD.

It is hypothesized that the rapid onset and anti-fibrotic activity of PFD, which have been observed in the treatment of IPF, will complement the delayed anti-inflammatory and immunosuppressive effects of MMF, to produce a significantly more rapid and/or greater improvement in lung function over time than occurs in patients receiving control therapy with MMFand Plac.

The Primary Objective is therefore to assess the impact of combined PFD and MMF, as compared to treatment with MMF alone (i.e combined with Plac), on the overall course of lung function over an 18-month course of therapy.

A secondary objective is to demonstrate that combination therapy with PFD and MMF is well tolerated, in comparison to MMF alone, and not associated with limiting toxicity that impacts on the overall treatment effect.

# 4 STUDY DESIGN AND ENDPOINTS

## 4.1 DESCRIPTION OF THE STUDY DESIGN

The SLS III study is designed as a Phase II multi-center, double-blind, parallel group, randomized and placebo-controlled clinical trial addressing the treatment of patients with active and symptomatic SSc-ILD. Enrollment will occur at 15 to 20 participating academic clinical centers within the United States. 150 patients who are either treatment-naïve or only recently started on treatment (≤6 mo of prior treatment with a potentially disease-modifying therapy) will be randomized in a 1:1 assignment to receive either oral MMF and Plac (acting as a control arm) or a combination of oral MMF and oral PFD (acting as an experimental arm), with both regimens administered for 18 months. The target dose for MMF will be 1,500 mg twice daily as tolerated, starting with 500 mg twice daily and proceding with a 4-step titration at monthly intervals until a maximal tolerated dose or the target dose is achieved for each patient. The target dose for PFD will be 801 mg three times daily as tolerated, starting with 267 mg three-times daily and proceding with a 3-step titration at 2 week intervals until a maximal tolerated dose or the target dose is achieved for each patient. The length of therapy, 18 months, was established based on prior studies with immunosuppressive therapy alone, which demonstrated that 18 months represents the time required to achieve a peak treatment response. The primary outcomes will include physiologic measures of lung function, HRCT imaging measures of lung inflammatory and fibrotic changes, dyspnea, assessments of skin inflammation and thickening, and patient reported measures of symptoms and quality of life. Tolerability and toxicity of the two treatments will also be assessed.

### 4.2.1 Primary Endpoint

The primary endpoint is the change from baseline, measured at 3-month intervals, in the mean forced vital capacity (represented as the percentage of the age-, height-, gender- and race-adjusted predicted value, i.e. FVC-%) over the course of the 18-month double-blind treatment period.

### 4.2.2 Secondary Endpoints

4.2.2.1 The change from baseline to 18 months, measured at 3-month intervals, in single-breath diffusing capacity for carbon monoxide (DLCO), calculated as a percent of the age-, height-, gender-, race- and hemoglobin-adjusted predicted value (DLCOHb-%).

4.2.2.2 The change from baseline to 18 months, measured at 3-month intervals, in the Modified Rodnan Skin Score (mRSS).

4.2.2.3 The change from baseline to 18 months, measured at 3-month intervals, in dyspnea, as measured by the Baseline and Transition Dyspnea Index (BDI and TDI, respectively.)

4.2.2.4 The change from baseline to 18 months, measured at 3-month or 6-month intervals, in Patient Reported Outcomes (PROs), which provide subjective measures of dyspnea and quality of life based on patient responses to standardized patient questionnaires which include:

a) St. George Respiratory Questionnaire (SGRQ); 3 month intervals

b) Health assessment questionnaire modified for scleroderma (SHAQ); 6 month intervals
c) Patient-reported outcomes measurement information system 29-item health profile (PROMIS-29 version 2.0); 6 month intervals

4.2.2.5 The change from baseline to 18 months in quantitative HRCT measures of SSc-ILD which specifically include:

a) Quantitative lung fibrosis score in the whole lung (QLF-WL).
b) Quantitative lung fibrosis score in the lobe of maximal involvement (QLF-LM).
c) Quantitative interstitial lung disease score in the whole lung (QILD-WL).
d) Quantitative interstitial lung disease score in the lobe of maximal involvement (QILD-LM).
e) Total lung capacity at maximum inspiration (HRCT-TLC)

4.2.2.6 Differences in the frequency distribution of individual patient responses when grouped into defined intervals of improvement or worsening (defined by the change in an outcome measure from baseline to 18 months) for the following outcome measures:

a) Forced vital capacity (represented as the percentage of the age-, height-, gender- and race-adjusted predicted value, i.e. FVC-%)
b) Single-breath diffusing capacity for carbon monoxide (DLCO), calculated as a percent of the age, height, gender-, race- and hemoglobin-adjusted predicted value (DLCOHb-%).
c) Modified Rodnan Skin Score (mRSS).
d) Transitional Mahler Modified Dyspnea Index (TDI)

4.2.2.7 The time (in months) required for each treatment arm to achieve a 3.0% or greater improvement from baseline in the FVC-% over the 18-month treatment period.

4.2.2.8 A threshold analysis based on the percentage of subjects in each treatment arm achieving greater than a 5% improvement from baseline in FVC-% over the 18-month treatment period.

4.2.2.9 Tolerability and toxicity of combined MMF and Plac vs MMF and PFD over the course of 18 months.

### 4.2.3 Other Important Endpoints

4.2.3.1 Physician and Patient Global Assessments

a) Physician global assessment of patient's "overall health" in the past week on a Likert scale; 6 month intervals
b) Physician transition questions comparing patient's i) overall health and ii) lung involvement to that at the baseline visit; 6 month intervals
c) Patient global assessment of "overall health" in the past week on a Likert scale; 6 month intervals
d) Patient transition questions comparing their i) overall health and ii) lung involvement to that at the baseline visit; 6 month intervals

4.2.3.2 UCLA Scleroderma Clinical Trial Consortium GIT 2.0 (UCLA SCTC GIT 2.0); 6 month intervals

4.2.3.3 Leicester Cough Questionnaire (LCQ); 6 month intervals

### 4.2.4 Exploratory Endpoints

Exploratory endpoints will include the following:

4.2.4.1 Identification of baseline features that predict treatment responsiveness, disease progression and the course of lung and skin disease over time.

4.2.4.2 Identification of biomarkers that predict disease features, treatment responsiveness, disease progression and the course of lung and skin disease over time.

4.2.4.3 Composite outcome measures that distinguish early and late treatment responses

4.2.4.4 Performance of CRISS index at 6, 12 and 18-months

# 5 STUDY ENROLLMENT AND WITHDRAWAL

## 5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible for randomization as a study patient, an individual must meet all of the following inclusion criteria. Notes are included, as needed, to provide additional explanation and/or background rationale for selected criteria (see bullet points). Patients will provide consent prior to the screening and screening is included as part of the consent process. Note that the screening occurs in stages in order to limit unnecessary testing:

<u>Screening criteria that must be met prior to moving forward to HRCT imaging</u>

5.1.1 Age ≥18 yrs

5.1.2 Scleroderma as determined by the 2013 ACR/EULAR classification criteria.

5.1.3 Grade ≥2 on the Magnitude of Task component of the Mahler Modified Dyspnea Index (Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing less than three flights of stairs, or carrying a light load on the level.

5.1.4 FVC-% of ≤85% at screening.

- NOTE: Inter-test variability for FVC-% can range up to 10% and therefore some participants with an FVC-% between 80-85% at screening might exceed an FVC-% of 85% when testing is repeated at the baseline.
- NOTE: The acceptable reproducibility of the FVC-% at baseline will be governed by inclusion criteria #7 detailed in Section 5.1.7 below.

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

- This criteria is based on the natural history SSc-ILD which is known to be more progressive early after the onset of scleroderma and become less active over time.

<u>Screening HRCT imaging</u>

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

- This criteria defines a population with active and measurable parenchymal lung involvement.

<u>Final screening criteria fulfilled at Baseline Visit, but prior to randomization</u>

5.1.7 Repeat FVC-% at the baseline visit within 10% of the FVC-% value measured at screening. 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.

## 5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study. The majority of exclusion criteria are assessed at screening, unless explicitly stated. Notes are included, as needed, to provide additional explanation and/or background rationale for selected criteria (see bullet points).

5.2.1 Disease features supporting the primary diagnosis of another connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus or mixed connective tissue disease (Features consistent with a secondary Sjogren syndrome or scleroderma-associated myopathy will be allowed).

5.2.2 FVC-% <45% at either screening or baseline.

- to avoid severe, probably irreparable disease associated with higher morbidity

5.2.3 FEV1/FVC ratio <0.65 at either screening or baseline.

- to avoid concurrent and clinically-significant obstructive lung disease which can increase the risk for infection, need for corticosteroid therapy, and interferes with use of spirometry as outcome measure

5.2.4 DLCOHb-% of <30% at screening or <25% at baseline.

a) All participants with a DLCOHb-% between 30 to 40% must have pulmonary artery pressures documented by either echocardiogram, right heart catheterization or magnetic resonance imaging in order to be considered for inclusion.

- the risk for concurrent scleroderma-related pulmonary vascular disease is increased in patients with higher FVC/DLCO ratios, warranting additional testing before including such subjects in the study.
- In order to account for normal test-to-test variability, subjects with an acceptable DLCOHb-% of between 30% to 40% at screening, with no evidence of clinically significant pulmonary hypertension, will remain eligible at their baseline measurement as long as the DLCOHb-% is $\geq$25**%** predicted**.**

5.2.5 Diagnosis of clinically significant resting pulmonary hypertension or mild pulmonary hypertension requiring treatment with more than one oral medication 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.
- The presence of mild pulmonary hypertension, identified as either an estimated right ventricular systolic pressure of </=40 mmHg on echocardiogram or mean systolic pulmonary artery pressure of </=30 mmhg on right heart catheterization is acceptable for inclusion in the study if there are no signs of right heart dysfunction and treatment

includes no more than one oral PAH medication.

5.2.6 Evidence of uncontrolled congestive heart failure, unstable ischemic heart disease, history of complicated pulmonary embolism impacting on heart or lung function, or unstable cardiac arrhythmia requiring chronic anticoagulation.

- to avoid undiagnosed scleroderma cardiomyopathy and unstable patients whose concurrent disease might impact on the measured study outcomes.

5.2.7 Clinically significant abnormalities on HRCT not attributable to SSc

- e.g., lung mass, cavitary lesion, airspace consolidation, mediastinal adenopathy, etc.

5.2.8 Hematologic abnormality at screening including:

a) Leukopenia (white blood cells [WBC] $<4.0x10^3/\mu l$)
b) Thrombocytopenia (platelet count $<120.0x10^3/\mu l$)
c) Clinically significant anemia [Hemoglobin (Hgb) <10.0 g/dl]

Participants with an identified and correctable etiology may be eligible if repeat testing within the maximal 90-day screening period meets all criteria.

- to avoid persistent bone marrow abnormalities or bleeding that would complicate detection and treatment of a primary side effect of MMF therapy.

5.2.9 A diagnosis of chronic liver disease or abnormal baseline liver function test (LFTs) or total bilirubin that are >2.0 x upper normal limit.

5.2.10 Serum creatinine >2.0mg/dl

5.2.11 History of recurrent aspiration, uncontrolled heartburn, or gastroesophageal reflux disease with a reflux scale score of >1.00 as determined by a UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Scale (UCLA SCTC GIT), Version 2.0.

Participants with uncontrolled heartburn or GERD that is amenable to medical management may be eligible if repeat testing within the maximal 90-day screening period meets this criteria.

- both medications can exhibit significant GI toxicity and it would be inappropriate to include patients already exhibiting clinically significant and uncontrolled GI symptoms.

5.2.12 Known achalasia, esophageal stricture or esophageal dysfunction sufficient to limit the ability to swallow medication.

- this trial requires that patients take a large number of capsules at frequent intervals throughout the day and these conditions represent significant obstacles to compliance.

5.2.13 Pregnancy (documented by serum pregnancy test) and/or breast feeding

5.2.14 If of child bearing potential (a female participant < 55 years of age who has not been postmenopausal for ≥ 5 years or who has not had a bilataeral salpingectomy, 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, unless the participant chooses abstinence (to avoid heterosexual intercourse completely). If a subject chooses abstinence, then a second reliable means of contraception is not needed.

5.2.15 Prior use of potential disease modifying antirheumatic drugs (DMARDs) according to the following exposure rules:

a) Use of oral cyclophosphamide (CYC), MMF, azathioprine or other oral or short half-life DMARDs (as detailed in Section 7.5.1a) for more than 6 months in the past year, as determined at the time of the initial screening visit.

b) Treatment with more than three intravenous doses of CYC, more than one course of Rituximab or other intravenous or injectable DMARDs (as detailed in Section 7.5.1b) in the past year.

c) ) More distant h/o treatment with a DMARD is allowed as long as the patient has a new diagnosis/new episode of active SSc-ILD since stopping that treatment and meets the criteria noted in 15a or 15b.

- these criteria have been adopted as the cut-off for enrolling treatment naïve patients as we are particularly focused on the contribution of early treatment on the study outcomes.

5.2.16 Use of CYC, MMF, azathioprine, Rituximab or other DMARD (as detailed in Section 7.5.1a&b) in the 30 days prior to the baseline visit unless the patient is on MMF and the responsible physician indicates that continued use is in the best clinical interest of the patient.

- the study focuses on treatment-naïve patients (as defined above) and a wash-out period from pre-study drugs with potential DMARD activity will help to clarify the contribution of early exposure to PFD on the treatment outcome.
- subjects who meet all other criteria, but have been on limited therapy with MMF and decide to participate, will be assessed by the responsible study physician to determine whether it is in the patient's best clinical interest to stop MMF and complete a 30-day washout period or to continue on pre-study drug therapy until the time of randomization.

5.2.17 Active infection (lung, ulcers or elsewhere) whose management would be compromised by immunosuppression.

5.2.18 Other serious concomitant medical illness (e.g., active malignancy within the past 5 years other than surgically-removed local skin cancer such as a basal cell carcinoma), chronic debilitating illness (other than SSc), unreliability or drug abuse that might compromise the patient's participation in the trial.

5.2.19 Current use, or use within the 30 days prior to their baseline visit, of prednisone (or equivalent) in doses >10 mg/day.

- to avoid increased drug toxicity due to combined immunosuppression.
- subjects who meet all other criteria, but have been on higher doses of prednisone, will be allowed to decrease their prednisone (or equivalent) dose and proceed to the baseline visit at the completion of the 30-day washout.

5.2.20 Smoking of cigars, pipes, or cigarettes during the past 6 months.

- to avoid the increased risk of pulmonary complications and variation in lung function that would be independent from the primary study objectives.

5.2.21 Use of contraindicated medications, including medications with putative disease-modifying properties that do not meet the exposure limits described in Exclusion Criteria #15 and #16, moderate or strong inhibitors of cytochrome P450 (CYP) isozyme 1A2 (CYP1A2) (note

ciprofloxacin allowed up to a dose of 500 mg twice daily), and moderate inducers of CYP1A2 (such as tobacco smoke or phenytoin). See Section 7.5 for complete list.

A study eligibility form will be completed at the end of screening and baseline (i.e., prior to randomization) to assure that all criteria have been met before a subject is eligible for randomization.

## 5.3 DISCONTINUING DRUG TREATMENT OR COMPLETE WITHDRAWAL FROM THE STUDY

Patients participating in this study may discontinue active drug treatment but continue with follow-up. They may also completely withdraw from the study (i.e. drop out; end their participation entirely).

### 5.3.1 Reasons for Discontinuing Drug Treatment or Withdrawing from Study

Patients participating in this study may discontinue active drug treatment or completely withdraw from the study (or their participation terminated) for the following anticipated reasons.

5.3.1.1 Ongoing participation in this research study is voluntary and patients may discontinue active drug treatment or completely withdraw from the study at any time without an identified cause or the need for explanation.

5.3.1.2 Patients may also discontinue or be removed from active drug treatment due toadverse events (AEs), laboratory abnormality, or other medical condition or situation such that continued use of one or both of the study drugs is not considered to be in their best interest.

5.3.1.3 Patients who become pregnant and/or start breast feeding; which are absolute contraindications to continued therapy, will be required to stop active drug therapy.

5.3.1.4 Patients who meet the pre-defined criteria for a “Treatment Failure” (see Section 5.3.2) will be withdrawn from the active drug treatment .

### 5.3.2 Definition and Handling of Treatment Failures

Subjects who, after >3 months of study, demonstrate an absolute fall in FVC-% of ≥ 15% from their baseline determination will be classified as “treatment failures” (e.g., an initial FVC-% of 75% would need to drop to ≤60% to be classified as a treatment failure). A treatment failure will also be defined, after >3 months of study, when the FVC-% falls below a lower limit of <35%, 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 an absolute decrement of ≥15% from baseline and/or a FVC-% of ≤ 35%. Subjects with treatment failures will be withdrawn from active drug treatment (both PFD/Plac and MMF). 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 and their request is reviewed and agreed to by the Executive Committee. Subjects who fail treatment will be encouraged to return for key outcome determinations at 12 and 18 months, at which time any medication prescribed by their treating physician since leaving the study will be recorded in addition to other required assessments for the 12 and 18-month visits.

### 5.3.3 Handling of Premature Participant Withdrawals

Should a participant prematurely discontinue all active drug treatment for any reason, he/she will be asked to return for key outcome determinations at 12 and 18 months. Their clinical management during the intervals between these visits will be at the discretion of the patient and their treating physician. At the 12 and 18 month visits, any medication prescribed by their treating physician since discontinuing study drug treatment will be recorded in addition to other required assessments for the 12 and 18-month visits. 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 as defined by the statistical plan.

If only PFD/Plac is prematurely discontinued, and the participant continues to take MMF according to the protocol, then they will continue their participation in all study visits according to the normal study protocol.

If MMF is prematurely discontinued, the participant must stop the PFD/Plac study medication as well and will be asked to return for key outcome determinations at 12 and 18 months. Their clinical management during the intervals between these visits will be at the discretion of the patient and their treating physician. At the 12 and 18 month visits, any medication prescribed by their treating physician since discontinuing study drug treatment will be recorded in addition to other required assessments for the 12 and 18-month visits.

Participants who completely withdraw from the study (drop out; end their participation entirely) will 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.

## 5.4 PREMATURE TERMINATION OR SUSPENSION OF STUDY

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 sponsors, Institutional Review Boards and the FDA.

The DSMB 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 may recommend at any time that the study should be terminated due to drug toxicity, patient safety, poor compliance and/or futility considerations. In such cases, their recommendations will be reviewed and discussed with the Executive Committee, which will make a final determination.

# 6 STUDY AGENT

## 6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

### 6.1.1 Source and Acquisition of Study Drugs

The Investigational Drug Section, Department of Pharmaceutical Services, University of California Los Angeles (UCLA) Ronald Reagan Medical Center will serve as the Pharmacy Core, providing centralized drug procurement, accountability and distribution for all study drugs (MMF, PFD) and the Plac.

6.1.1.3 **Mycophenolate Mofetil (MMF)** will be purchased from a generic vendor, Teva Pharmaceuticals, Inc., or other generic vendor authorized to market by the FDA

In the event that the commercial drug supply from Teva is insufficient to meet the needs of the study at any point in time, MMF will be acquired from an alternative manufacturer approved by the FDA to produce and sell equivalent 250 mg capsules. Participating study sites and impacted patients will be advised of any change in appearance of the capsules, bottles and labeling without other required change to the Protocol.

6.1.1.2 **Pirfenidone (PFD)** will be shipped directly by the manufacturer, Genentech, Inc., to the UCLA Pharmacy Core.

6.1.1.3 **Placebo (Plac),** formulated to match PFD and manufactured by Genentech, Inc., will be shipped directly to the UCLA Pharmacy Core.

### 6.1.2 Study Agent Formulation, Appearance, Packaging and Labeling

All study agents used in this protocol will be provided in sealed and clearly identified bottles from their respective manufacturers and stored by the UCLA Pharmacy Core for distribution to the participating clinical site research pharmacies without modification or relabeling.

On-site, at the Clinical Site Research Pharmacy, patient specific labeling will be added to the existing MMF bottles when supplied as 500 capsule bottles from the manufacturer. Alternatively, when supplied as 100 capsule bottles, bottles derived from the same lot will be transferred at the time of dispensing into a single generic bottle to produce bottles of 500 capsule each. In such cases, labels containing both drug information and patient specific identification and instructions will be applied. Use of existing bottles is not a concern for this study drug as it will be provided in an open-label format to study participants. However, in order to maintain the blind and avoid disclosure due to the manufacturer labeling, capsules from individual bottles of PFD and Plac must be transferred at the time of prescription into new generic bottles and fresh labels attached by the site pharmacy. In addition to patient specific labeling information, the information from the study label will be replicated except that the contents will indicate capsules that contain either “267 mg of PFD or matching Plac”.

6.1.2.1 **Mycophenolate Mofetil (MMF)**

Formulation and strength: Size 1 hard opaque gelatin capsules containing 250 mg
Appearance: Opaque capsules, Blue and Orange
(Teva example, coloring will vary by manufacturer)
Packaging: Supplied in Bottles of either 100 capsules (NDC 0093-7334-01) or 500 capsules (NDC 0093-7334-05) with barcodes and labels

(Teva example, labeling will vary by manufacturer)


6.1.2.2 **Pirfenidone (PFD)**

Formulation and strength: Size 1 hard opaque gelatin capsules containing 267 mg
Appearance: Opaque, White
Packaging: Labeled for investigational use only, marked as Pirfenidone on bottle
Supplied in Bottles of 270 capsues with labeling as follows:

| Bottle label text (translation in local language) |
|---|
| **[ Protocol no. ]**<br>**270 hard capsules pirfenidone 267 mg placebo**<br>For oral use only.<br>**Use as directed by your doctor.**<br>Batch no.: xxxxxxx<br>Pat.no.:_____<br>Investigator:_____<br>Dispensing date:_____<br>**Do not store above 30°C.**<br>Keep out of reach of children.<br>Return empty packaging and unused products.<br>For clinical trial use only.<br>[ Sponsor; e.g. Roche ] F. Hoffmann-La Roche Ltd, 4070 Basel, Switzerland |

6.1.2.3 **Placebo (Plac)**

Formulation and strength: Size 1 hard opaque gelatin capsules containing 267 mg
Appearance: Opaque, White
Packaging: Labeled for investigational use only, marked as Plac on bottle
Supplied in Bottles of 270 capsues with labeling as follows:

| Bottle label text (translation in local language) |
|---|
| **[ Protocol no. ]**<br>**270 hard capsules pirfenidone 267 mg placebo**<br>For oral use only.<br>**Use as directed by your doctor.**<br>Batch no.: xxxxxxx<br>Pat.no.:_____<br>Investigator:_____<br>Dispensing date:_____<br>**Do not store above 30°C.**<br>Keep out of reach of children.<br>Return empty packaging and unused products.<br>For clinical trial use only.<br>[ Sponsor; e.g. Roche ] F. Hoffmann-La Roche Ltd, 4070 Basel, Switzerland |

### 6.1.3 Product Storage & Stability

Prefilled and sealed bottles will be shipped from the manufacturers with labeled expiration dates; beyond which they will not be used in the study. MMF capsules will be stored at room temperature; defined as between 68°F (20°C) to 77°F ( 25°C). PFD and Plac capsules will also be stored at room temperature; defined in this case as between 68°F (20°C) to 86°F ( 30°C). Brief excursions in temperature allotted for shipping and handling.

### 6.1.4 Route, Administration, Titration Schedule and Target Dose

6.1.4.1 Drug: **MMF**: 250 mg hard gelatin capsules
Route: Oral, taken without food and at least one hour prior to taking a PPI.
Titration Schedule and Target Dose (as tolerated):

| Dose | # of Capsules | Schedule | Dose Duration |
|---|---|---|---|
| 500 mg | 2 | Twice daily | 4 weeks |
| 1000 mg | 4 | Twice daily | 4 weeks |
| 1250 mg | 5 | Twice daily | 4 weeks |
| 1500 mg | 6 | Twice daily | Duration of study |

Randomized patients who were on pre-study treatment with MMF, and for whom it was determined that they should continue on treatment without a 30-day washout period, will be evaluated by the responsible study physician and start their MMF study drug titration at one of the following doses:

a) if their pre-study dose matches one of the levels indicated above and they are tolerating the dose, they may be started at the same dose level. This dose level should be administered for the initial 4 weeks of the study and then titrated as indicated by the table above.

b) if their pre-study dose does not match one of the levels indicated above, they may start at the level that is closest to but does not exceed their pre-study dose. They will continue on that dose for the initial 4 weeks of the study and then have drug titrated as indicated by the table above.

c) at the discretion of the responsible study physician, the study patient may be started at a dose that is lower than their pre-study dosing if it is determined to be in the best

clinical interest of the patient. They will continue on that dose for the initial 4 weeks of the study and then have drug titrated as indicated by the table above.

6.1.4.2 Drug: **PFD**: 267 mg hard gelatin capsules
Route: Oral, taken with food
Titration Schedule and Target Dose (as tolerated):

| Dose | # of Capsules | Schedule | Dose Duration |
|---|---|---|---|
| 267 mg | 1 | Three times daily | 2 weeks |
| 534 mg | 2 | Three times daily | 2 weeks |
| 801 mg | 3 | Three times daily | Duration of study |

6.1.4.3 Drug: **Plac**: 267 mg hard gelatin capsules
Route: Oral, taken with meals
Titration Schedule and Target Dose (as tolerated):

| Dose | # of Capsules | Schedule | Dose Duration |
|---|---|---|---|
| 267 mg | 1 | Three times daily | 2 weeks |
| 534 mg | 2 | Three times daily | 2 weeks |
| 801 mg | 3 | Three times daily | Duration of study |

### 6.1.5 Pre-specified Dose Adjustment & Modifications

The toxicity profiles for MMF and PFD are well established as outlined in Section 2.3 and drug discontinuation and/or dose modification should be managed in a manner consistent with the following criteria in order to provide a nearly uniform response to pre-defined toxicity at all centers. However, in clinical situations that fall outside of these parameters and if warranted based on good clinical practice, a site investigator may independently modify drug dosing as needed to assure patient safety. If such a change is required, the reasons for the deviation are to be documented and the Executive Committee notified within 3 days. Medications that are contraindicated while on treatment with the study drugs are detailed separately in Section 7.5.

In the event that one study drug is permanently discontinued due to tolerability, adverse event or other medical consideration, then continued use of the remaining study drug will be according to the following pre-specified management:

- If only PFD/Plac is permanently discontinued, the participant may continue to take MMF according to the protocol and continue their participation in all study visits according to the normal protocol-defined schedule of events.
- If MMF is prematurely discontinued, the participant must stop the PFD/Plac study medication as well and will be asked to return for key outcome determinations at 12 and 18 months as detailed in Section 5.3.3 ( Handling of Premature Participant Withdrawals).

6.1.5.1 **Pre-specified dose adjustments for MMF.**

The following abnormalities and laboratory test monitoring results require study drug adjustment, 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.

a) Allergic reaction associated with the administration of MMF.

Dose Management: Study drug will be stopped and subject withdrawn from study.

b) Evidence of clinically significant Bone Marrow Suppression including any one or more of the following
   - WBC <2.5x$10^3$/µl
   - Absolute neutrophil count <1.0x$10^3$/µl
   - Platelet count <100.0x$10^3$/µl
   - Hemoglobin < 10.0 gm/dl or a drop in hemoglobin to < 9.0 gm/dl if the baseline hemoglobin was < 11.0 gm/dl

   Dose Management: Management as follows:
   - Hold study drug until there is a stabilization of the hematologic abnormality at a value above the toxicity threshold levels indicated above. In addition, if other causes of noted reductions are identified (e.g., gastrointestinal bleeding), they should be treated and stabilized before restarting on study drug.
   - Once threshold levels are exceeded (an indication of recovery), MMF will be reintroduced at a daily dose of 1000 mg (500 mg twice daily doses) and inceased by 500 mg (one 250 mg capsule for each of the twice daily doses) every two weeks. At the discretion of the clinical site investigator, 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 of MMF taken by the patient or one capsule per-dose less (500 mg/day less).
   - In the event of repeat toxicity, the same cycle should be repeated except with the intention of achieving a maintenance dose equal to 1000 mg/day less for MMF.

c) Documentation of gastrointestinal ulcer, bleeding or abdominal emergency.

   Dose Management: Management as follows:
   - Hold study drug until there is a clinically stable resolution of the problem. In addition, if other causes of noted conditions are identified (e.g., polyps, diverticulitis, untreated peptic ulcer disease), they should be treated and stabilized before restarting on study drug.
   - Once a stable recovery occurs, as judged by the clinical site investigator, MMF will be reintroduced at a daily dose of 1000 mg (500 mg twice daily doses) and inceased by 500 mg (one 250 mg capsule for each of the twice daily doses) every two weeks. At the discretion of the clinical site investigator, 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 of MMF taken by the patient or one capsule per-dose less (500 mg/day less).
   - In the event of repeat toxicity, the same cycle should be repeated except with the intention of achieving a maintenance dose equal to 1000 mg/day less for MMF.

d) Pregnancy or initiation of breastfeeding.

   Dose Management: Study drug will be permanently discontinued and subject withdrawn from study.

e) Serum creatinine > 2.0 mg/dl or estimated GFR to $\leq$ 40 ml/min/1.73 $m^2$ (corrected) in the absence of other etiology.

Dose Management: Hold study drug until there is a clinically stable resolution of the problem. In addition, if other causes of noted conditions are identified (e.g., medications, dehydration, etc.), they should be treated and stabilized before restarting on study drug. If there is no improvement, the study drug will be stopped and subject withdrawn from study.

f) Ongoing infection whose management would be significantly compromised by continued drug-associated immunosuppression or any hospitalization, surgery or infection requiring antibiotic therapy where the immununosuppressive effects of MMF are determined by the clinical site investigator to likely complicate the patient's response to therapy.

Dose Management: Hold study drug 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.

g) Development of a proven malignancy other than basal cell cancer of the skin or cervical carcinoma in situ removed entirely by excisional biopsy or surgical resection.

Dose Management: Study drug will be permanently discontinued and subject withdrawn from study.

h) Any adverse event felt by the investigator to be possibly or probably related to the administration of MMF and of a clinical significance sufficient to warrant holding or discontinuing drug.

Dose Management: Management as follows:

- Hold study drug until there is a clinically stable resolution of the problem. In addition, if other causes of noted conditions are identified, they should be treated and stabilized before restarting on study drug.
- Once a stable recovery occurs, as judged by the clinical site investigator, MMF will be reintroduced at a daily dose of 1000 mg (500 mg twice daily doses) and inceased by 500 mg (one 250 mg capsule for each of the twice daily doses) every two weeks. At the discretion of the clinical site investigator, 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 of MMF taken by the patient or one capsule per-dose less (500 mg/day less).
- In the event of repeat toxicity, the same cycle should be repeated except with the intention of achieving a maintenance dose equal to 1000 mg/day less for MMF.
- Alternatively, for less severe or dangerous adverse events (e.g., dyspepsia) not responding to concomitant medications: the study drugs may be discontinued at the discretion of the clinical site investigator until the adverse event disappears. At that point the subject can be restarted at one-half of the original dose. The subject can return to the full dose of MMF after 2 weeks or 500 mg less (one capsule less for each of the twice daily doses) as clinically indicated. All such discretionary plans for adjusting study drug dosing should be approved within 3 days of initiation by the Executive Committee.

i) Unresolved toxicity or inability to tolerate therapy with MMF for $\geq$60 days.

Dose Management: Study drug will be permanently discontinued and subject withdrawn

from the treatment phase of the study.

6.1.5.2 **Pre-specified dose adjustments for PFD/Plac.**

The following abnormalities and laboratory test monitoring results require study drug adjustment, 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.

a) For liver enzyme elevations in a patient who exhibits ≥2 but ≤3x the upper limit of normal (ULN) for ALT and/or AST without clinical symptoms or hyperbilirubinemia after starting PFD/Plac therapy.

Dose Management: Management as follows:

- Any confounding medications that might increase liver function tests should be discontinued and any other potential causes identified and treated.
- Liver function tests should be performed at 7-14 day intervals to monitor.
- Continue the current dose of study drug and then choose one of the following two managments based on the follow-up liver function test results:
  i. If liver function tests worsen to >3X ULN, then follow recommendations as noted in b), c) or d) below.
  ii. If liver function tests are stable or show improvement (or continued improvement) on repeat testing in 7-14 days, then the study drug should be continued at the current dose.

b) For liver enzyme elevations in a patient who exhibits >3 but ≤5 × the ULN for ALT and/or AST without clinical symptoms or hyperbilirubinemia after starting PFD/Plac therapy.

Dose Management: Management as follows:

- Any confounding medications that might increase liver function tests should be discontinued and any other potential causes identified and treated.
- Liver function tests should be performed at 7-14 day intervals to monitor as needed based on resulting laboratory and clinical findings.
- Choose one of the following two managments based on the results of repeat liver function testing:
  iii. If liver function tests worsen (but still do not exceed 5 x ULN) on repeat testing in 7-14 days despite addressing any confounding medications or causes, then the study drug should be held until liver function tests have decreased to ≤2X normal. PFD/Plac should then be re-started at one capsule three times daily, re-titrated using the original study titration protocol (see Section 6.1.4.3) and increased up to the full dosage as tolerated.
  iv. If liver function tests are stable or show improvement (or continued improvement) on repeat testing in 7-14 days, then the study drug may be handled using one of two options at the discretion of the clinical site investigator:
    - continue at the current dosage without interruption and continue to monitor at 7-14 day intervals.
    - reduce the PFD/Plac dose by 1 capsule for each of the three times daily doses and continue to monitor at 7-14 day intervals.

c) For liver enzyme elevations in a patient who exhibits >3 but ≤5 × ULN for ALT and/or AST that is accompanied by clinical symptoms or hyperbilirubinemia after starting PFD/Plac therapy.

Dose Management: Study drug will be permanently discontinued and subject withdrawn from study.

d) For liver enzyme elevations in a patient who exhibits >5 × ULN for ALT and/or AST after starting PFD/Plac therapy.

Dose Management: Study drug will be permanently discontinued and subject withdrawn from study.

e) For gastrointestinal symptoms that are of sufficient clinical importance to warrant drug dose adjustment (typically involving nausea, diarrhea, vomiting, and dyspepsia), the patient should take the following steps, if not already in place and clinically indicated, prior to considering dose management:

- Take the study medication with food.
- Spread the dose throughout the meal rather than taking all capsules at once.
- Add appropriate pharmacologic therapy to control acid and dysmotility.

Dose Management:.

- Reduce PFD/Plac dose by 1 capsule for each of the three times daily doses and if symptoms improve/resolve, can increase back to the original dosing after 2 weeks as tolerated. If the higher dose is still not tolerated, then 1 capsule less for each of the three times daily doses can be continued.
- Reduce PFD/Plac dose by 1 capsule for each of the three times daily doses and if symptoms do not improve, the study drug should be held until the potential interaction with the medical condition in question has resolved. Once the patient is stable, the study drug can be re-started and titrated according to the original schedule as tolerated.

f) For photosensitivity skin reactions or rash that do not respond to UVA/UVB sunscreen, sun avoidance, and/or the use of over the counter topical corticosteroid creams, and are of sufficient clinical importance to warrant drug dose adjustment.

Management:.

- Reduce PFD/Plac dose by 1 capsule for each of the three times daily doses and if symptoms improve/resolve, can increase back to the original dosing after 2 weeks as tolerated. If the higher dose is still not tolerated, then 1 capsule less for each of the three times daily doses can be continued.
- Reduce PFD/Plac dose by 1 capsule for each of the three times daily doses and if symptoms do not improve, the study drug should be held until the potential interaction with the medical condition in question has resolved. Once the patient is stable, the study drug can be re-started and titrated according to the original schedule as tolerated.

g) An infection whose management requires the use for Ciprofloxacin at a dose of 750 mg twice daily (or other fluoroquinolone at high dose) for 2 weeks or less will require a dose adjustment for PFD/Plac.

- During the course of antibiotic treatment, the daily dose of PFD/Plac should be reduced by 1 capsule three times a day during the period of concommitent use

(patients on 3 capsules should reduce to 2, while patients on 2 capsules should reduce to 1).

h) Any adverse event felt by the investigator to be possibly or probably related to the administration of PFD/Plac and of a clinical significance sufficient to warrant adjusting or discontinuing drug.

Dose Management: Management as follows:

- Reduce PFD/Plac dose by 1 capsue for each of the three times daily doses and if symptoms improve/resolve, can increase back to the original dosing after 2 weeks as tolerated. If the higher dose is still not tolerated, then 1 capsule less for each of the three times daily doses can be continued as the maximally tolerated treatment dose.
- Alternatively, at the discretion of the site investigator, the study drugs may be held at the discretion of the clinical investigator until the adverse event disappears. PFD/Plac should then be re-started and using the standard titration protocol increased to the full dosage as tolerated.

i) Unresolved toxicity or inability to tolerate therapy with PFD/Plac for ≥60 days.

Dose Management: Study drug will be permanently discontinued and subject withdrawn from the treatment phase of the study.

### 6.1.6 Duration of Therapy

The intended duration of therapy for all study drugs is 18 months.

### 6.1.7 Tracking of Dose and Drug Compliance

The protocol proposes several challenges to effective drug administration due to the combination of two therapies administered according to different schedules, with different titration protocols, and with multiple capsules required for each dose. Compliance is further challenged by differences in whether the drugs are taken with or without food.

As a result of these challenges, specific attention will be focused on the use of study aides to promote the correct timing, amount and administration of the study drugs. The following procedures will be used to promote patient compliance and allow drug compliance monitoring.

6.1.7.1 **Patient aides to promote compliance:**

a) Wallet-size Study Drug Identification Cards will be prepared at each study visit that describe the current dose and schedule of each drug to be taken during the coming study interval until the next scheduled visit.
b) Study Drug Administration Calendars with daily check-boxes will be generated for patients at each study visit to map out and record each dose of each study drug when taken.
c) “One-Week Drug Dispensers” will be provided to the patients and they will be taught how to fill them at each visit, and at home on a weekly basis, so that medications are easily and reliably dispensed without having to count out capsules and remember each dose. Two dispensers will be provided: a) a twice daily dispenser for MMF and b) a three-times daily dispenser for PFD/Plac.
d) An SLS III Study Bag will be provided to subjects and they will be instructed to put all study drugs and records into this bag (study drug bottles, pill organizers, study folder with drug

calendars, etc.) and carry it with them to/from every clinic visit.

6.1.7.2 **Study approaches promoting the monitoring of drug compliance:**

a) Individual drug inventory records will be kept for each patient, recording number of bottles and capsules dispense and the number returned at the next visit.
b) Mandatory pill/capsule counts of unused medication will be required at each visit and reconciled with the patients drug usage calendar.

## 6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

### 6.2.1 Responsibilities of the Central Pharmacy Core

The UCLA Pharmacy Core will be responsible for maintaining a central log of all drug purchased and received, that in storage, and that distributed to every participating clinical site. The Pharmacy Core will be responsible for reordering and restocking of drug inventory and for timely distribution to all participating sites to assure that study needs never lapse. They will also be responsible for tracking lot expiration and replacement.

### 6.2.2 Responsibilities of the Clinical Site Pharmacy

The dispensing pharmacy at each site will maintain an independent drug accountability log for all shipments from the UCLA Pharmacy Core that will act as an automatic drug reconciliation control for the Core Pharmacy. In addition, logs will be maintained to track each bottle dispensed, the date, number of capsules and study recipient.

### 6.2.3 Site Investigator Responsibility

The site team will maintain a drug accountability log for each study patient to document subject number, visit number, date medication dispensed, number of bottles and bottle ID, number of capsules dispensed at each visit and the number counted as remaining at the subsequent visit. All used bottles will be returned and stored on site until an inventory control is carried out by the study monitor.

### 6.2.4 Monitoring & Compliance Oversight by the Data Coordinating Center

The Data Coordinating Center will utilize an online recording and reconcilliation system to track these three inventory sources and acurately track and verify the status of all study drugs. Errors and discrepencies between the different reporting sources will be reconciled as part of the individual site monitoring process carried out by the DCC. Compliance will be calculated for each visit and for each subject from the information supplied in this manner.

# 7 STUDY PROCEDURES AND SCHEDULE

## 7.1 STUDY PROCEDURES/EVALUATIONS

In the event of an emergency that disrupts patient or institutional access and usual study care, such as an unexpected disaster or pandemic, refer to **Protocol Section 17.0** (EMERGENCY DISASTER/ PANDEMIC MANAGEMENT PLAN) for allowable adjustments to the study procedures and schedule that may be invoked as dictated by the nature of the emergency.

### 7.1.1 Study Specific Procedures

7.1.1.1 **Spirometry**. Spirometry will be 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 (15). All spirometry equipment and procedures will conform to the most recently published standards of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force (34,41). 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 Forced Expiratory Volume in the first second (FEV1). Printouts of all data and curves will be sent to the Pulmonary Function Core at UCLA for central quality control monitoring with individual optimization and re-training for study specific requirements at each site if required to assure standardized and reproducible measurements. Spirometry results will be expressed both as measured values and as a percentage of gender-specific predicted values using the regression equations of Hankinson (17) for spirometry. For spirometry, the race-specific regression equations of Hankinson (17) will be used for African-Americans and Mexican-Americans and normal referenced values multiplied by 0.88 for Asians (17a). Spirometry measurements will be performed at entry (screening), just prior to initiation of study medication (baseline) and every 3 months for the entire 18 months of the study.

In the event that a participant has already completed spirometry testing within 30 days of Screening Visit #1 and the testing meets all eligibility criteria, it may be used in lieu of repeating the spirometry measurements at Screening Visit #1. In order to be considered eligible, the testing must have been performed at the same facility that will be used during the study, the full spirometry data set must be available for review and it must pass a Quality Assurance review by the Pulmonary Function Core at UCLA.

7.1.1.2 **Single-breath diffusing capacity for carbon monoxide (DLCO) and DLCO adjusted for hemoglobin (DLCOHb)**. DLCO measurements will be performed in accordance with published ATS/ERS guidelines using equipment and testing techniques that meet ATS/ERS requirements (33). At least 2 acceptable tests that meet repeatability criteria (33) will be performed and the mean DLCO value (uncorrected for Hgb) from acceptable measurements reported. Other reported values will include the inspired vital capacity, which must be within 10% of the expiratory Vital Capacity, and the alveolar volume. DLCO will then be corrected for hemoglobin that will be measured at the corresponding study visit as part of the blood monitoring and reported as DLCOHb. DLCO and DLCOHb will be expressed both as measured values and as a percentage of gender-specific predicted values (DLCO-% and DLCOHb-%) using the regression equations of Neas (37). The race-specific equations of Neas et al. (53) will also be used for calculation of the predicted values of DLCO for African-Americans. DLCO measurements will be performed at entry (screening), just prior to initiation of study medication (baseline) and every 3 months for the entire 18 months of the study.

In the event that a participant has already completed DLCO testing within 30 days of the Screening Visit #1 and the testing meets all eligibility criteria, it may be used in lieu of repeating the DLCO measurements at Screening Visit #1. In order to be considered eligible, the testing must have been performed at the same facility that will be used during the

study, the full DLCO data set must be available for review and it must pass a Quality Assurance review by the Pulmonary Function Core at UCLA.

7.1.1.3 **Thoracic HRCT with Quantitative Image Analysis**. Thoracic HRCT will be performed using a standardized volume acquisition protocol developed by the UCLA Imaging Core with 1-1.5 mm slice thicknesses acquired contiguously. Multidetector CT scanners with 16 to 64 channel scanners will be used at each site to minimize breath-hold times (4-6 seconds). The subject will be imaged prone and at suspended end-inspiration (HRCT-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." Subjects will be instructed how to signal when their lungs are completely full and the technologists will again remind them to hold their breath for the entire scan. Digitalized imaging data collected during the scan is transferred from the clinical site to the UCLA HRCT QIA Core using HIPAA compliant electronic transfer protocols and stored on a dedicated server with built-in encryption security and automated backup in place.

Within the UCLA HRCT QIA Core, scans are reconstructed and entered into a quantitative image workstation to produce quantitative scores. The imaging analysis process consists of three steps: (1) semi-automated lung segmentation which requires approval by a radiologist; (2) execution of an automated classification model that classifies pixels into fibrotic, ground glass, honeycomb and normal lung patterns within the segmented whole lung region; and (3) division of the entire lung into anatomical lobes. HRCT scores for quantitative lung fibrosis (QLF), quantitative ground glass opacifications (QGG) and quantitative honeycomb changes (QHC) are determined separately from the percentage of overall pixels in which the classified abnormal pattern comprised reticular opacity with architectural distortion (QLF), hazy parenchymal opacity through which normal lung markings were visible in the absence of reticular opacity or architectural distortion (QGG) or clustered air-filled cysts with dense walls (QHC), respectively. The quantitative ILD (QILD) score represents the sum of all abnormally classified scores (QLF+QGG+QHC). Scores are then summated for the whole lung (WL; e.g. QLF-WL) which includes all pixels within both lungs, and for the lobe of maximal involvement (LM; e.g. QLF-LM). These approaches have been well standardized and reported for the evaluation of SSc-ILD, with documented changes in response to immunosuppression with both cyclophosphamide and MMF (27-28,52). Total lung capacity will also be determined from the image analysis protocol and is known to be highly correlated with plethysmographic measures of total intrathoracic gas volume measured by spirometric techniques. Defined CT outcome measures will therefore include at a minimum:

a) Quantitative lung fibrosis score in the whole lung (QLF-WL).
b) Quantitative lung fibrosis score in the lobe of maximal involvement (QLF-LM).
c) Quantitative ground glass opacification score in the whole lung (QGG-WL).
d) Quantitative ground glass opacification score in the lobe of maximal involvement (QGG-LM).
e) Quantitative honeycomb change score in the whole lung (QHC-WL).
f) Quantitative honeycomb change score in the lobe of maximal involvement (QHC-LM).
g) Quantitative interstitial lung disease score in the whole lung (QILD-WL).

h) Quantitative interstitial lung disease score in the lobe of maximal involvement (QILD-LM).
i) Total lung capacity at maximum inspiration (HRCT-TLC)

The UCLA HRCT QIA core will screen the thoracic HRCT performed during screening 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. Scans with abnormal findings will be reported to the site investigators and reconstructed images obtained at the local site will be available for review by clinical radiologists at the site outside of the responsibility of the study protocol.

A radiation physicist from the UCLA HRCT QIA Core will initially assess the equipment and perform standardization protocols using phantom image results obtained at each site prior to the initiation of clinical testing. Site equipment will be programmed with the study-specific protocols to assure safety and reproducibility. 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 18-month study, for a total radiation exposure of 240 millirem.

In the event that a participant has recently undergone an HRCT scan of the chest that was performed outside of the study, but within the required time window prior to randomization (≤ 60 days), it may be considered as a potential substitute for the official screening HRCT. To be eligible for such use, the digitalized imaging data collected during the scan must be transferred from the clinical site to the UCLA HRCT QIA Core using HIPAA compliant electronic transfer protocols as already noted. A review will be carried out to determine whether it was performed in a manner consistent with the key requirements for a full study scan performed at TLC, whether the image quality is adequate for assessing required inclusion and exclusion criteria, and whether digital image analysis can be adequately performed to yield required study outcome data as already described. If the scan is determined to be adequate by the UCLA HRCT QIA Core then it will be submitted for assessment in lieu of repeating the scan and exposing the patient to additional radiation. If it is determined that the scan is not adequate by these criteria, the patient may decide whether to proceed with a full protocol-defined HRCT in order to continue with the study screening.

7.1.1.4 **Mahler Baseline and Transitional Dyspnea Index**. The paper version of Mahler's Baseline Dyspneic Index (BDI) will be administered to subjects by a trained interviewer at the time of the baseline visit and the Translational Dyspneic Index (TDI) will be administered to subjects by a trained interviewer every 3 months thereafter. The interviewer will have an advanced understanding of dyspnea in respiratory disease and training in how to ask questions and select, based on information provided by the patient, from pre-defined test responses. If at all possible, the same person will conduct all evaluations for a given patient. The TDI has proven to be a sensitive measure of treatment response in both SLS I and II studies (25,51).

7.1.1.5 **Skin thickness and function scores.** Skin thickness score will be quantified using the modified Rodnan measurement method (mRSS), with a scale that ranges from 0 (no skin involvement) to 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 (7-8). Skin thickness scores have been found to significantly improve when therapy with cyclophosphamide was compared to placebo in SLS I (50-51) and similar improvements in response to MMF were confirmed in SLS II which likely contribute to the overall treatment effect (52). The capacity for PFD to enhance the effects of therapy with MMF on skin disease in patients with SSc is currently unknown and will be specifically evaluated as a component of this study using the mRSS assessment. The mRSS will be performed at baseline and at 3 month intervals throughout the study and should be carried out by the same investigator (if at all possible).

7.1.1.6 **Composite end point.** Combined Response index in Systemic Sclerosis (CRISS). CRISS, a combined outcome index to assess treatment responses in SSc, was developed through an iterative process combining expert consensus conferences and data-driven approaches, and was recently validated as a therapeutic outcome measure (21). This composite index is a 2-step process where step 1 assesses clinically meaningful decline in cardio-pulmonary-renal involvement and step 2 assesses changes in mRSS, FVC-%, patient global assessment, physician global assessment, and HAQ DI (from the SHAQ) as a combined outcome measure. It will be assessed at 6-, 12, and 18 month period.

7.1.1.7 **Physician and Patient Global Assessment.** The Physician Global Assessment employs a 0-10 likert scale to assess the patient's "overall health" in the past 1 week. The single-item question is anchored from 0 (excellent health) to 10 (extremely poor). In addition, the physician will assess changes in the patient's overall health and lung involvement by transition questions: Compared to the baseline visit, how would you rate your patient's i) overall health and ii) overall lung involvement: *much better, a little better, no change, a little worse, much worse*. Using a similar approach the Patient Global Assessment employs a 0-10 likert scale for the patient to assess their overall health in the past 1 week. The single-item question is anchored from 0 (excellent health) to 10 (extremely poor). In addition, the patient will assess changes in the patient's overall health and lung involvement by transition questions: Compared to your baseline visit, how would you rate your i) overall health and ii) overall lung involvement: *much better, a little better, no change, a little worse, much worse*. Global Assessments will be administered at baseline (no transition component) and every 6 months thereafter.

7.1.1.8 **Patient Reported Outcomes (PROs) in the form of patient responses to standardized patient questionnaires.** A spectrum of validated questionnaires will be used to assessed patient related outcomes that include disease specific, overall health, and their perspectives on symptoms, performance and quality of life (Complete questionnaire can be found in Appendix A):

a) St. George's Respiratory Questionnaire (SGRQ): SGRQ, 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 (5). 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.

b) Health assessment questionnaire modified for scleroderma (SHAQ): The SHAQ will be administered at baseline and every 6 months thereafter. The SHAQ was shown to be favorably responsive to CYC therapy in SLS I (26).
c) Patient-reported outcomes measurement information system 29-item health profile (PROMIS-29). The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) roadmap initiative utilized a cooperative group approach to develop and standardize item banks to measure patient-reported outcomes relevant across medical conditions. The resulting PROMIS-29 instrument provides assessment scales for Physical Functioning, Anxiety, Depression, Fatigue, Pain Interference, Sleep Disturbance and Impact on Social Roles, and has been validated to measure health status outcomes in patients with SSc while requiring limited time to repeat (average <2 min) (18). It will be administered at baseline and every 6 months thereafter.
d) UCLA Scleroderma Clinical Trial Consortium GIT 2.0. The UCLA SCTC GIT is a validated 36-item, self-reported measure assessing bowel involvement, symptoms and related emotional well-being, and social functioning administered at baseline, 6 months, 12 months, 18 months (23-24). A modified version, including only questions #1-8, will be used at screening to determine study eligibility as related to the extent of GI symptoms.
e) Leicester Cough Questionnaire (LCQ): This self-administered 19-item questionnaire for the quantitative assessment of symptoms of cough frequency and severity will be completed at baseline and every 6 months (30). This will be supplemented with a ranking of cough severity, frequency, and sputum production using a simple likert scale (42,53).

7.1.1.9 **Blood collection for the Biological Specimen Repository**. Blood samples will be serially collected from each study patient prior to (baseline), during (at 12 months) and at the completion of therapy (18 months). These samples will be immediately processed on site into serum, plasma, buffy coat and whole blood RNA samples (PAXgene RNA collection) according to a standard protocol, labeled and temporarily stored at the site at ≤ -70°C prior to batch shipping to a central repository for long-term storage. The Bio-specimen Repository will reside at the University of California, Los Angeles, where a master inventory will be kept of all samples. The Executive Committee will oversee all requests (both internal and external to the study) to access these samples for ancillary biological studies directed toward the understanding of scleroderma, SSc-ILD, and the treatment protocol.

7.1.1.10 **Study drug reconciliation.** A drug inventory is kept for every patient and contains the date, lot number, bottle number, type (MMF vs PFD/Plac) and number of capsules released to the patient. Patients are also provided with a medication calendar to complete and bring back at each visit and are required to return with all bottles of study drug that are in their possession regardless of whether they are opened, in use or empty. Bottle and pill counts will occur at each visit and information recorded on the drug inventory.

7.1.1.11 **Assessment of adverse events.** As detailed in Section 8

### 7.1.2 Standard of Care Study Procedures

7.1.2.1 **Complete medical history and physical examination**. A complete medical history and physical exam covering details related to the patient's history of scleroderma, their entire medical history with a review of systems, and their current physical findings will be

performed during the initial screening visit and at 12 months. This will include a review of pertinent medical records provided by the patient and/or their referring physicians.

7.1.2.2 **Focused Interval history and examination**. A review of current symptoms, medications, physical findings and any changes noted by the patient or a physician since a prior visit will be performed at baseline, monthly for the first 6 months and then every 3 months.

7.1.2.3 **Vital signs.** Vital signs will include: pulse, blood pressure, respiratory rate, temperature ($^{o}$C), weight (kg), and SpO2 by pulse oximetry will be performed at initial screening, baseline , monthly for the first 6 months and then every 3 months. Height (cm) will only be done at screening.

7.1.2.4 **Toxicity Monitoring with Blood Tests**. A comprehensive set of laboratory results performed on a current blood sample to evaluate any toxicity or adverse events associated with Scleroderma or its treatment with the study drugs. Blood tests will include: comprehensive metabolic panel (to include serum electrolytes, BUN, Cr, glucose, albumin, ALT, AST, alkaline phosphatase, bilirubin, total protein) and a complete blood count with differential (to include WBC, Hgb, hematocrit, platelet count, and cellular differential count including absolute neutrophil count). Monitoring will occur at initial screening, monthly for the first 6 months and then every 3 months.

In the event that a participant has had all required laboratory tests completed within 30 days of the Screening Visit #1, the results may substitute for the official screening laboratory tests.

7.1.2.5 **Pregnancy Testing**. An initial serum pregnancy test at screening and subsequent monitoring with urine pregnancy testing to be performed on all female participants of child-bearing potential at baseline, monthly for the first 6 months and then every 3 months.

## 7.2 STUDY SCHEDULE

The complete schedule for study visits is detailed below and summarized in the subsequent Study Flow Diagram (**Figure 7.3a**) and Table of Study Visits (see below Schedule of Events, **Table 7.3a**).

In the event of an emergency that disrupts patient or institutional access and usual study care, such as an unexpected disaster or pandemic, refer to **Protocol Section 17.0** (EMERGENCY DISASTER/ PANDEMIC MANAGEMENT PLAN) for allowable adjustments to the study procedures and schedule that may be invoked as dictated by the nature of the emergency.

### 7.2.1 Screening Visits (Study Day -90 through 0; Screening Visit #1&2)

In order to be eligible for randomization, patients must proceed through a series of screening steps. At Screening Visit #1, a preliminary evaluation is performed and if eligibility criteria are met the patient will proceed to the screening HRCT scan (Screening Visit #2) to assess for the presence of any ground glass opacity and to exclude concurrent findings of concern that may require additional evaluation or exclude the patient from further participation. If all inclusion and exclusion criteria are met, the patient will proceed to the baseline evaluation where a final check of pulmonary function and pregnancy testing is required to meet randomization criteria:

7.2.1.1 **Screening Visit #1.** (preferably within 60 d, but no earlier than 90 d prior to randomization)

a. Patient provides written informed consent and research HIPAA authorization prior to any evaluation or testing.

b. A review of existing medical records and tests, provided by the patient or referring physician, is performed to document the history of scleroderma and general medical history.
c. Vital signs obtained.
d. The patient undergoes a complete medical history and physical examination.
e. Review of concomitant medications including all medications taken within past 3 months and any prior use of medications detailed in Section 7.5.1 (Prohibited Medications & Treatments with Potential Disease Modifying Effects).
f. Pulmonary function testing for spirometry and diffusing capacity will be completed unless acceptable testing has been completed within 30 days of the screening visit and approved in advance by the Pulmonary Function Core at UCLA.
g. A limited subset of the UCLA SCTC GIT questionnaire (including only Questions #1-8) is completed by the participant
h. The patient has blood drawn for monitoring blood tests and serum pregnancy test (if applicable).

7.2.1.2 **Screening Visit #2.** (may not be completed until results from screening visit #1 confirm potential eligibility, must be completed within 60 days of randomization)
a) Thoracic HRCT with visual review for the presence of entry and exclusion criteria and with Quantitative Image Analysis

### 7.2.2 Enrollment/Baseline Visit (Study Day 0; Visit #1)

Subjects who meet all defined inclusion and exclusion criteria (up to this point) will be asked to return for the baseline visit. This will preferably occur within 60 days of their initial screening evaluation, but must occur within 90 days of their initial evaluation. For subjects who have not met study enrollment criteria, their participation will end and they will not proceed. The following studies will take place at the baseline visit.

a) A focused interval history and examination will be performed.
b) Vital signs obtained.
c) Review of concomitant medications
d) Pulmonary function testing for spirometry and diffusing capacity will be completed.
e) Urine pregnancy test performed (if indicated)
f) Patient Reported Outcomes (PROs) in the form of patient responses to standardized patient questionnaires (SGRQ; SHAQ; PROMIS-29; UCLA SCTC GIT; LCQ).
g) Complete the Mahler Baseline Dyspnea Index.
h) An assessment of skin thickness and function scores (mRSS)
i) Patient and Physician Global Assessments (no transition questions)
j) Blood collection for the Biological Specimen Repository

If the repeat FVC-% fails to be within 10% of the value obtained at screening or is not > 45% and ≤ 85%, the subject will be offered one opportunity to repeat testing within 7 days. If they choose not to repeat testing or if the repeat testing remains outside of the required range, their participation in the study will end.

If the subject meets the repeat FVC-% inclusion criteria, and assuming that pregnancy testing is negative if required, the site coordinator will complete the online eligibility case report form and login to the electronic web-based randomization application to randomize the participant.
Once randomization has occurred, the UCLA Pharmacy Core or the designated site Pharmacy, will confirm the drug and bottle assignment. In conjunction with a prescription signed by the Clinical Site

investigator, study drugs will be dispensed according to established protocol. Randomization will occur via the Data Coordinating Center and result in a notification of study assignment group to the UCLA Pharmacy Core and the Site Pharmacy. Study drug (PFD/Plac) will be released in a double-blinded manner and neither the study investigators or staff, or the patient, will know the treatment assignment.

### 7.2.3 Follow-up Visits (Months 0.5-18, Study Visits #2-21)

There are a number of potential side effects of the study drugs that may be detected only through regular follow-up and blood testing monitoring. Given the nature of the study drugs, good clinical practice will require study visits for the purpose of monitoring every month for the first 6 months and every 3 months thereafter until drug therapy is completed at month 18. In addition to this clinical monitoring, outcome assessments are scheduled to occur every 3 to 6 months throughout the duration of the study. Finally, additional contact will be maintained with the subjects through regularly scheduled phone contacts to assure that drug titration and dosing, changes in health and adverse events are adequately tracked and recorded.

#### 7.2.3.1 **Regular Follow-up Visits (Months 1 through 18; Visits 3, 5-9, 12, 15, 18, 21).**

Regular follow-up visits include a combination of toxicity monitoring and outcome assessments. Not all assessments are performed at each visit. Therefore, after each task listed below, a list of visit numbers (and corresponding month on study drug) is included to indicate when the task will be performed. Each visit must be completed within a specified time window with respect to the protocol defined follow-up date: Visit #3 = ±7d; Visits #5-9 and 12 = ±10 d; Visit #15, 18, 21 = ±14d.

a) A focused interval history and examination will be performed.
[Visit # 3 (month 1), 5-9 (months 2-6), 12 (month 9), 18 (month 15), 21 (month 18)]
b) Vital signs obtained.
[Visit # 3 (month 1), 5-9 (months 2-6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]
c) Assessment of adverse events
[Visit # 3 (month 1), 5-9 (months 2-6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]
d) Review of concomitant medications
e) Study drug reconciliation
[Visit # 3 (month 1), 5-9 (months 2-6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]
f) Study drug dispensing
[Visit # 3 (month 1), 5-9 (months 2-6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]
g) Toxicity monitoring with blood tests.
[Visit # 3 (month 1), 5-9 (months 2-6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]
h) Urine pregnancy test performed (if indicated)
[Visit # 3 (month 1), 5-9 (months 2-6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]
i) Pulmonary function testing for spirometry and diffusing capacity will be completed.
[Visit #6 (month 3), 9 (months 6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]

j) Patient Reported Outcomes (PROs) in the form of patient responses to standardized patient questionnaires
   - SGRQ
     [Visit #6 (month 3), 9 (month 6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]
   - SHAQ; PROMIS-29; UCLA SCTC GIT; CRISS; LCQ
     [Visit #9 (month 6), 15 (month 12), 21 (month 18)]

k) Complete the Mahler Transitional Dyspnea Index.
   [Visit #6 (month 3), 9 (months 6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]

l) An assessment of skin thickness and function scores (mRSS)
   [Visit #6 (month 3), 9 (months 6), 12 (month 9), 15 (month 12), 18 (month 15), 21 (month 18)]

m) Physician and Patient Global Assessments.
   [Visit #9 (month 6), 15 (month 12), 21 (month 18)]

7.2.3.2 **Additional Assessments at the 12-Month & 18 Month Visit (Visit #15 and 21).**

a) In addition to testing completed at the Regular Follow-up Visits described above, the following will take place at the 12 Month Visit:
   - Blood collection for the Biological Specimen Repository
   - The patient undergoes a complete medical history and physical examination.

b) In addition to testing completed at the Regular Follow-up Visits described above, the following will take place at the 18 Month Visit:
   - Blood collection for the Biological Specimen Repository
     Thoracic HRCT with Quantitative Image Analysis

7.2.3.3 **Phone Follow-up Visits.**

**Month 0.5 (Visit #2); Month 1.5 (Visit #4); Months 7-8 (Visit #10-11); Months 10-11 (Visit #13-14); Months 13-14 (Visit #16-17); Months 16-17 (Visits 19-20)**
**(Visit windows ±7d for Visits 2 & 4; ±10d for all others)**

a) Focused interval history
b) Assessment of adverse events
c) Review of Concomitant medications
d) Study drug reconciliation (focused review of current dose and changes since last visit, missed doses, remaining supply)

### 7.2.4 Final Phone Follow-up Visit / Early Termination Final Phone Visit

**Month 19 (Visit #22) or within 30 days of completely withdrawing from study**
**(Visit window ±10d)**

a) Focused interval history
b) Assessment of adverse events
c) Review of medications and alternative treatments (if premature termination visit)
d) Reasons for leaving study (if premature termination visit)

### 7.2.5 Follow-up for Participants who Prematurely Discontinue Study Drug Treatment or who Completely Withdraw from the Study

Should a participant prematurely discontinue all study drugs he/she will be asked to return for the key outcome determinations at 12 and 18 months, as detailed above. In addition, at that time, any medication prescribed by their treating physician since discontinuing study drugs will be recorded.

The participant will also be asked to participate in an exit visit as detailed in 7.2.4 above. Should the participant die, the cause of death will be determined and recorded if possible.

In the event that one study drug is permanently discontinued due to tolerability, adverse event or other medical consideration, then continued use of the remaining study drug will be according to the following pre-specified management:

- If only PFD/Plac is permanently discontinued, the participant may continue to take MMF according to the protocol and continue their participation in all study visits according to the normal protocol-defined schedule of events.
- If MMF is prematurely discontinued, the participant must stop the PFD/Plac study medication as well and will be asked to return for key outcome determinations at 12 and 18 months as detailed in Section 5.3.3 ( Handling of Premature Participant Withdrawals)

### 7.2.6 Unscheduled Visits for Additional Safety Monitoring

As detailed in Protocol Section 8 on Safety, patients who experience defined adverse events that require additional safety monitoring will be asked to return at defined intervals for additional follow-up and blood test monitoring (if indicated). It is estimated that routine laboratory safety monitoring may be required every 1-2 weeks until the side effect is resolved or until a proper dose of medication is identified.

### 7.2.7 Long-term Follow-up

On a voluntary basis, as a component of the consent process, participants will be asked whether they are willing (or not) to be contacted on an annual basis for up to 5 years after completing the study protocol at which time they would be asked to provide an update regarding their health status, symptoms related to their scleroderma and to describe any other treatments that they might have received for this condition.

## 7.3 SUMMARY OF STUDY SCHEDULE AND ASSESSMENTS

**Figure 7.3a Study Schedule Flow Diagram**

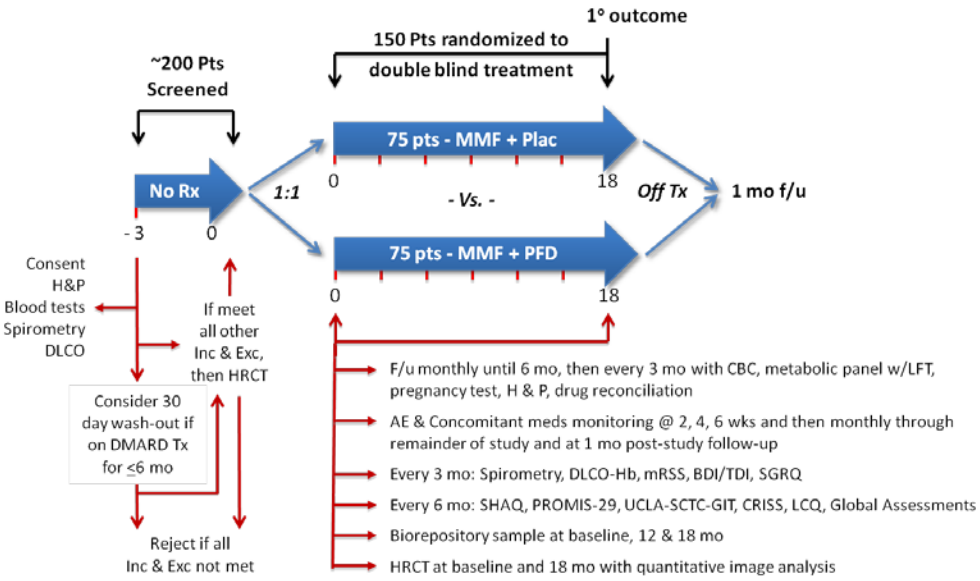


**Table 7.3a: Table of Study Visits & Assessments**

***SCREENING AND INITIAL 6 MONTHS***

| Type of Visit: | Screen | Baseline | Phone | Regular | Phone | Regular | Regular | Regular | Regular | Regular |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #:** | **S1-2** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| **Study Month:** | | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 5 | 6 |
| **Assessments** | | | | | | | | | | |
| Medical history | X | X | X | X | X | X | X | X | X | X |
| Physical exam | X | X | | X | | X | X | X | X | X |
| Vital signs** | X | X | | X | | X | X | X | X | X |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X |
| Medication Reconciliation | X | X | X | X | X | X | X | X | X | X |
| Adverse events | | | X | X | X | X | X | X | X | X |
| Lung function testing | X | X | | | | | X | | | X |
| Blood Test Monitoring | X | | | X | | X | X | X | X | X |
| Questionnaires | UCLA SCTC GIT | X | | | | | X | | | X |
| HRCT scan of chest | X | | | | | | | | | |
| Pregnancy test* | X | X | | X | | X | X | X | X | X |
| Blood for Bio-Repository | | X | | | | | | | | |

* For women who are able to become pregnant; require a blood test at screening then urine testing.

** Only need height at screening.

***MONTHS 7 – 19 & EXTRA VISITS***

| Type of Visit: | Phone | Regular | Phone | One Year | Phone | Regular | Phone | 18 Month | Final Phone | Extra |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #:** | **10-11** | **12** | **13-14** | **15** | **16-17** | **18** | **19-20** | **21** | **22** | |
| **Study Month:** | 7, 8 | 9 | 10, 11 | 12 | 13, 14 | 15 | 16, 17 | 18 | 19 | Yrs 2-5 |
| **Assessments** | | | | | | | | | | |
| Medical history | X | X | X | X | X | X | X | X | X | X |
| Physical exam | | X | | X | | X | | X | | |
| Vital signs** | | X | | X | | X | | X | | |
| Concurrent Medication | X | X | X | X | X | X | X | X | X | X |
| Medication Reconciliation | X | X | X | X | X | X | X | X | | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X |
| Lung function testing | | X | | X | | X | | X | | |
| Blood test monitoring | | X | | X | | X | | X | | |
| Questionnaires | | X | | X | | X | | X | | |
| HRCT scan of chest | | | | | | | | X | | |
| Pregnancy test* | | X | | X | | X | | X | | |
| Blood for BioRepository | | | | X | | | | X | | |

* For women who are able to become pregnant; require a blood test at screening then urine testing.
** Only need height at screening.

## 7.4 CONCOMITANT MEDICATIONS & TREATMENTS DURING THE STUDY

All concomitant prescription, over-the-counter and non-prescription medications taken during study participation will be recorded on the case report forms (CRFs) and checked for compatibility with the study drugs as defined in Section 7.5.

## 7.5 PROHIBITED MEDICATIONS AND TREATMENTS DURING THE STUDY

### 7.5.1 Prohibited Medications & Treatments with DMARD Activity

Medications from the following list, and their biosimilars, are prohibited and may not be taken prior to screening in amounts (or for time intervals) that exceed allowable limits as detailed in Exclusion Criteria #15 and #16. They may not be taken while participating in the active drug treatment phase of this study (except for MMF and PFD when specifically administered as study drugs according to the study protocol).

Prior use of these medications must be consistent with Exclusion Criteria #15

a) Oral or short half-life drugs with potential DMARD activity

- Anakinra
- Apremilast
- Azathioprine
- Baricitinib
- Cyclophosphamide oral
- Cyclosporine
- Dasatinib
- Imatinib
- Leflunomide
- Methotrexate
- Mycophenolate mofetil
- Nilotinib
- Nintedanib
- Pirfenidone
- Pomalidomide
- Rilonacept
- Tacrolimus
- Tofacitinib

b) Intravenous or injectable drugs with potential DMARD activity

- Abatacept
- Adalimumab
- Alemtuzumab
- Belimumab
- Canakinumab
- Certolizumab
- Cyclophosphamide IV
- Etanercept
- Guselkumab
- Golimumab
- Infliximab
- Ixekizumab
- Rituximab
- Sarilumab
- Secukinumab
- Tocilizumab
- Ustekinumab

### 7.5.2 Prohibited Medications & Treatments that may Increase Immune Suppression Risk

a) Prednisone >10mg/day (or equivalent corticosteroid).

**NOTE:** a brief pulse of prednisone to $\leq$30 mg/day that lasts no more that 7 days before returning to a dose of $\leq$ 10 mg is permissible if indicated for a temporary intercurrent medical condition.

a) Live vaccines administered within 30 days of, or after randomization including:
- Bacillus of Calemett and Guerin (BCG) Vaccine
- Measles Virus
- Mumps

- Polio Virus
- Rotovirus
- Rubella
- Small pox
- Typhoid
- Varicella Virus
- Yellow Fever
- Live influenza vaccine

### 7.5.3 Prohibited Medications that may Interfere with Study Drug Absorption/Metabolism

a) Antacids containing Magnesium and Aluminum Hydroxides ***should not*** be taken together (at the same time) with MMF due to their impact on the absorption of MMF.
**NOTE:** Antacids may be used, but should not be taken within 2 hrs of MMF.

b) Proton Pump Inhibitors (PPIs) ***should not*** be taken together (at the same time) with MMF due to their impact on the absorption of MMF.
**NOTE:** PPIs may be used, but should not be taken within 2 hrs of MMF.

c) Sevelamer and other calcium free phosphate binders ***should not*** be taken together (at the same time) with MMF due to their impact on the absorption of MMF.
**NOTE:** Calcium free phosphate may be used, but should not be taken within 2 hrs of MMF.

b) Cholestyramine ***should not*** be taken due to interference with enterohepatic recirculation of MMF

c) Cyclosprine ***should not*** be taken due to interference with enterohepatic recirculation of MMF

d) Norfloxacin and Metronidazole ***should not*** be taken together as a combination therapy while on therapy with MMF due to interference with serum levels of MMF

e) Ciprofloxacin and/or Amoxicillin plus Clavulanic Acid may temporarily interfere with the enterohepatic recirculation of MMF producing temporary reductions in serum MMF levels.
**NOTE:** Temporary use for 2 weeks or less is of unclear significance but sustained use of these antibiotics is not recommended.

f) Ciprofloxacin and other Fluoroquinolones which are moderate inhibitors of CYP1A2 may interfere with the metabolism of PFD, significantly increasing drug exposure.
**NOTE:** Use of Ciprofloxacin at a maximal dose of 500 mg twice daily for up to two weeks is allowed.
**NOTE:** If temporary use for Ciprofloxacin at a dose of 750 mg twice daily (or other fluoroquinolone at high dose) is required for 2 weeks or less, the daily dose of PFD should be reduced by 1 capsule three times a day during the period of concommitent use (patients on 3 capsules should reduce to 2, while patients on 2 capsules should reduce to 1)

g) Rifampin may temporarily interfere with serum levels of MMF.
**NOTE:** Temporary use for 2 weeks or less is of unclear significance but sustained use of these antibiotics is not recommended.

h) Fluvoxamine, enoxacin or other strong CYP1A2 inhibitors ***should not*** be taken due to their impact on the metabolism of PFD, which can significantly increase drug exposure

i) Smoking, which is a strong inducer of CYP1A2, is not allowed during the study

### 7.5.4 Restrictions on Medications with Other Adverse Interactions

a) Hormonal contraceptives may not be effective during administration of MMF due to interactions with drug metabolism and a second type of contraception must be used to participate in study if one of the following hormonal contraceptive is used:
   - Levongogrestrel
   - Norethindrone
   - Mestranol
   - Norgestrel
   - Ethinyl estradiol
   - Etonogrestrel

b) Use of tanning beds or medical phototherapy that includes UV light exposure are contraindicated during the use of PFD due to their impact on photosensitivity reactions.

## 7.6 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

**Prophylactic use of topical sunblock agents:** PFD is associated with photosensitivity. In addition to advising patients to wear protective clothing, hats, and avoid extended sun (or tanning light) exposure, they will be advised to use over the counter sunblock as a prophylactic therapy if sun exposure is anticipated.

**Prophylactic consumption of PFD with food:** Patients are advised to take PFD with food to help decrease gastrointestinal side effects.

# 8 ASSESSMENT OF SAFETY

## 8.1 SPECIFICATION OF SAFETY PARAMETERS

Safety parameters will include frequency of events and/or incidence of study subjects experiencing events, by study arm for the following:

a) Study-defined Treatment failures
b) Study-defined Treatment emergent AEs of Special Interest
c) All treatment emergent AEs, total and by organ system classification
d) All treatment related AEs, total and by organ system classification
e) All treatment emergent SAEs, total and by organ system classification
f) All treatment related SAEs, total and by organ system classification
g) All treatment emergent deaths
h) All treatment-emergent AEs and SAEs that result in discontinuation of treatment
i) Time to treatment failure, treatment emergent AEs and SAEs that result in discontinuation of treatment, and death

### 8.1.1 Definition of Adverse Events (AEs)

Adverse event means any untoward medical occurrence, such as an abnormal laboratory finding, physical sign, symptom, or diagnosis of a disease state, that is temporally associated with the use of an interventional treatment or procedure in a human subject regardless of whether or not it is considered intervention-related [consistent with 21 CFR 312.32 (a)].

8.1.1.1 **Treatment-emergent AEs (TEAEs):**

TEAEs are those that start or worsen after the start of study treatment and up to 7 days (for AEs) and 30 days (for serious AEs) after the last dose of study treatment. This AE definition would include the following:

- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of the study treatment administration
- Complications resulting from protocol-mandated procedures
- AEs occurring as a result of product withdrawal, abuse or overdose
- A change in a laboratory variable if considered by the investigator to be clinically significant or if it is caused (or should have caused) the investigator to reduce or discontinue the use of the product or initiate a non-protocol therapy or procedure

8.1.1.2 **AEs of Special Interest:**

AEs of Special Interest represent a specific subset of all AEs and are defined by the study protocol based on two distinct features: 1) their likely association with the investigational drug(s), and 2) the presence of pre-specified study drug management guidelines that are to be followed when the AE occurs.

### 8.1.2 Definition of Serious Adverse Events (SAEs)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. [Consistent with 21 CFR 312.32 (a)]

### 8.1.3 Definition of Unanticipated Problems (UP – unexpected AEs & Problems)

An AE or suspected adverse reaction is considered "unanticipated" if it is not listed or characterized in the Package Insert or in the current Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated

from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. [Consistent with 21 CFR 312.32 (a)]

## 8.2 CLASSIFICATION OF AN ADVERSE EVENT

### 8.2.1 Severity of Event

The intensity of all AEs will be graded using a five-point grading scale in which the following descriptions of severity will apply. Note that for some AEs, Grades 4 and/or 5 may not be applicable. In those cases only 3 different grades (Grade 1-3) are to be considered:

| | | |
|---|---|---|
| 8.2.1.1 | **Grade 1:** | "Mild"; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 8.2.1.2 | **Grade 2:** | "Moderate"; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*. |
| 8.2.1.3 | **Grade 3:** | "Severe"; medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. |
| 8.2.1.4 | **Grade 4:** | "Life-threatening consequences"; urgent intervention indicated. |
| 8.2.1.5 | **Grade 5:** | "Death related to AE". |

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### 8.2.2 Relationship to Study Drug

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. A binary assessment (related/not related) will be made and take into consideration the natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors. While the relationship to the study drug (related/not related) is part of the documentation process, it is not a factor in determining what is or is not reported in the study. All AEs are recorded regardless of relatedness.

| | | |
|---|---|---|
| 8.2.2.1 | **Related** | The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE. An AE can be deemed related even if other factors may have contributed to the event. |
| 8.2.2.2 | **Not Related** | There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established or appears to provide a plausible explanation |

(e.g. the participant's clinical condition, underlying disease or concomitant treatments).

### 8.2.3 Expectedness

For all SAEs, the Clinical Site Principal Investigator, in consultation with a designated Medical Monitor whenever possible, will be responsible for determining whether the SAE is expected or unexpected using the definition from section 8.1.3 above.

### 8.2.4 AE of Special Interest

AEs meeting the following criteria will be classified and reported as AEs of Special Interest in addition to their inclusion in the overall frequency and incidence of AEs.

- Leukopenia, defined as WBC $\leq 2.5 \times 10^3/\mu l$ of blood
- Neutropenia, defined as an absolute neutrophil count $< 1.0 \times 10^3/\mu l$ of blood
- Clinically significant anemia, defined as blood hemoglobin < 10.0 gm/dl or a drop in hemoglobin to < 9.0 gm/dl if the baseline hemoglobin was < 11.0 gm/dl
- Liver enzyme elevations that exceed 3× the upper limit of normal (ULN) ALT and/or AST.
- New onset or worsening of existing gastrointestinal symptoms that do not respond to medical management and are of sufficient clinical importance to warrant drug dose adjustment (including nausea, diarrhea, vomiting, and dyspepsia).
- Documentation of gastrointestinal ulcer, gastrointestinal bleeding or abdominal emergency
- Infection requiring hospitalization, intravenous antibiotics, or judged as requiring the withdrawal of immune suppression for effective treatment.
- New or reactivated viral infections including PVAN, JC virus associated PML, CMV infections, reactivation of HBV or HCV.
- Photosensitivity skin reactions that do not respond to sunscreen, avoidance, and as-needed use of over the counter topical creams, and are of sufficient clinical importance to warrant drug dose adjustment.
- Development of a proven malignancy other than basal cell cancer of the skin or cervical carcinoma in situ removed entirely by biopsy.
- Angioedema

## 8.3 ADVERSE EVENT REPORTING

A consistent methodology for eliciting AEs will be used at all subject evaluation time points that includes open-ended questions such as:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while

on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study (in frequency, severity or character), it will be recorded as an AE and a descriptor will be used as a modifier term to convey that it relates to a pre-existing condition that has changed (e.g. "more frequent headaches"). UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Principal Investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and to Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

### 8.3.1 Adverse Event Reporting

All AEs will be mapped to system organ classes (SOC) using preferred MedDRA SOC terms, graded for severity and relationship to study drugs as detailed above, and recorded with start dates occurring any time after informed consent is obtained until at least 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. A record of all AEs, by study subject and preferred SOC terms will be recorded centrally by the DCC.

### 8.3.2 Serious Adverse Event Reporting

All SAEs will be mapped to system organ classes (SOC) using preferred MedDRA SOC terms, graded for severity and relationship to study drugs as detailed above, and recorded with start dates occurring any time after informed consent is obtained until 30 days after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of SAEs since the last visit and study participants and their significant others will be asked in advance to notify the study investigators immediately regarding any hospitalization, serious change in their health or in the event of a death. Events will be followed for outcome information until resolution or stabilization, with stop dates recorded for resolution.

Regardless of whether the SAE is deemed related to use of the study agents, the data for the SAE must be reported with the appropriate information by the study investigators or their designee to the Data Coordinating Center within 24 hours of learning of the event. In addition, new follow-up data must be reported within 24 hours of receipt. The designated study medical monitor or designee may be contacted at any time for immediate discussion regarding such an event.

Hospitalizations for the following reason, which are not related to an AE, do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions.

Deaths occurring in patients who have withdrawn from the active treatment phase of the study will not be considered SAEs if the death occurs more than 30 days after last dose of study treatment. When recording a death, the event or condition that caused or contributed to the fatal outcome

should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, the report will be identified as an "Unexplained Death".

Investigators must report all SAEs to their governing IRB/IEC, as required by local regulations and guidelines.

A record of all SAEs, by study subject and preferred SOC terms will be recorded centrally by the DCC.

### 8.3.3 Unexpected Adverse Event/Problem (UP) Reporting

All adverse events that meet the definition of an UP should be reported to the local governing IRB within specific timelines as described below: The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken orare proposed in response to the UP.

8.3.3.1 **Reporting to the IRB required within 10 working days:**

- Any internal or external adverse event (UP) which meets all of the following criteria:
  a) Unexpected (in occurance, severity or in frequency of occurance that was not previously known and/or described in the approved informed consent document or other protocol related documents),
  b) and Related or possibly related to the research participation,
  c) and places subjects or others at greater risk of harm than was previously known or recognized (i.e. a serious adverse event, a new or increased risk to subjects/others)

8.3.3.2 **Reporting within 3 working days:**

- An SAE, including subject death, that meet all of the following criteria:
  a) Occurred in an interventional study (i.e., involving a drug, biologic, device procedure and/or behavioral interventions),
  b) Unexpected,
  c) and judged to be related or possibly related to research participation

### 8.3.4 Reporting of Pregnancy

a) Pregnancies should be reported from the time the patient signs the informed consent until 30 days after the last dose of study drug. Study treatment must be immediately discontinued if a patient becomes pregnant. Although pregnancy is not considered an SAE, a report should be completed and expeditiously submitted to the DCC and to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur.Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

#### 8.3.5 Reporting of Post-Study Adverse Events

SAEs occurring more than 30 days after a subject has completed or discontinued study participation, if reported to a study investigator and attributed to prior study drug exposure, will be reported as an SAE to Genentech, Inc. Any investigator who becomes aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, will report such event as an SAE to Genentech.

## 8.4 STUDY HALTING RULES

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 appointed DSMB 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 may recommend at any time that the study should be terminated due to drug toxicity, patient safety, poor compliance and/or futility considerations. In such cases, their recommendations will be reviewed and discussed with the Executive Committee, which will make a final determination.

## 8.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a 3-member External Data and Safety Monitoring Board (DSMB, See Section 15.1.5) composed of individuals with the appropriate expertise in SSc-ILD, the study drugs and/or clinical trials research including experts in Rheumatology, Pulmonary Medicine, Internal Medicine and/or Bioethics, and Biostatistics. The DSMB Chair will be appointed by the Study Executive Committee from among experts in the field who are not otherwise actively involved in the conduct of the Clinical Study or its reporting or analysis and who do not have a salaried appointment with any of the participating institutions. The DSMB Chair will then recommend the remainder of the Committee Members for consideration by the study Executive Committee using similar expertise and affiliation criteria.

The DSMB will review the protocol and recommend modifications with respect to monitoring, safety and outcome assessments that will be addressed by the study prior to the onset of clinical activity. Once the trial is initiated, the DSMB will review cumulative trial results to evaluate the treatment for beneficial and adverse effects, including the review of all AEs, SAEs and UP. The board will also monitor the performance of individual clinics and study performance indicators (drug monitoring and compliance, visit compliance, recruitment, etc.). The DSMB will meet every 6 months by teleconference and/or web videoconferencing for the duration of the trial and will interact directly with the Data Coordinating Center for access to study data and interim reports, and with the Executive Committee regarding any recommendations for procedural changes, study modifications or management of perceived safety or data integrity issues.

#### 8.5.1 Morbidity and Mortality Committee

A separate Morbidity and Mortality Review Committee (MMRC) will be appointed by the Executive Committee and consist of the Medical Monitor and two invited members who are not otherwise involved in the research. The composition of the MMRC will include at least one member specializing in pulmonary medicine and one in rheumatology. The purpose of this committee will be to review all reported SAEs (as detailed in Sections 8.1 to 8.3) and provide an independent and blinded determination as to:

a) The proximate cause of the SAE.
b) Relationship of the SAE to the study drug as detailed in Section 8.2.2.
c) The expectedness of the SAE as defined in Section 8.1.3.

Individual SAE case reports will be reviewed as they occur by an identified medical monitor who will assure that all relevant material has been collected and, in consultation with the reporting site investigator, that the determination of the proximate cause, relationship to the study drug and determination of expectedness are consistent with the documentation and reporting guidelines.

Independent reviews by the MMRC will occur retrospectively, in batches, at a time when the records for a group of 12-20 SAEs are ready for review or at the conclusion of the study if less than 12 SAEs are recorded. Each member of the MMRC will independently review cases and provide a determination. No further review will be required when all reviewers agree as to the relationship of the SAE to the study drug and the expectedness. Cases in which reviewers disagree on these determinations will be discussed at a MMRC teleconference and a final determination reported as either a consensus opinion (when all three reviewers agree after discussion) or a majority opinion (indicating the majority opinion of two out of three reviewers). The MMRC findings will represent the final study determination with respect to reporting SAE outcomes.

# 9 CLINICAL MONITORING

Throughout the course of the study, data will be monitored for accuracy and completeness and study procedures will be monitored for adherence to the protocol and Good Clinical Practices (GCP). In addition to frequent contacts through e-mail and telephone, on-site monitoring visits will be coordinated by the Statistical Analysis of Biomedical and Educational Research (SABER) unit at the University of Michigan. SABER (the Data Coordinating Center for this study) will be responsible for operational aspects and monitoring of the trial, including at least annual monitoring visits and/or remote source data verification.

The clinical monitor will ensure that:

- Data collected and entered into the database are verifiable against source documents for the participants. The clinical monitor will need access to subject medical records and other study-related records needed to verify the entries on the electronic case report forms.
- Appropriate consent is obtained for each participant prior to study procedures.
- The rights and well-being of participants are being protected.
- The study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol), with any other study agreements, with GCP and with applicable regulatory requirements.

- Study medication is properly dispensed and accounted for. The study monitor will also perform drug accountability checks and review the clinical site's regulatory document binder to assure completeness of documentation in all respects of clinical study conduct.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 STATISTICAL AND ANALYTICAL PLANS

A statistical analysis plan (SAP) will be written for the study that contains detailed descriptions of the analyses to be performed. The SAP will be finalized prior to unblinding of the data.

## 10.2 STATISTICAL HYPOTHESES

The primary hypothesis is that the rapid onset and anti-fibrotic effects of PFD, which have been observed in the treatment of Idiopathic Pulmonary Fibrosis (IPF), will complement the delayed anti-inflammatory and immunosuppressive effects of MMF, to produce a significantly more rapid and/or greater improvement in lung function over time than occurs in patients receiving control therapy with MMF (and Plac) alone. Statistically, the following null and alternative hypotheses will test the superiority of the combination of PFD+MMF versus MMF+Plac in improving the change from baseline in mean forced vital capacity (as a percentage of the age-, height-, gender- and race-adjusted predicted value, indicated as FEV-%) over the course of the 18-month double-blind treatment period (primary endpoint):

$H_0$: $\Delta_{PFD+MMF} = \Delta_{MMF+Plac}$

$H_A$: $\Delta_{PFD+MMF} \neq \Delta_{MMF+Plac}$

where Δ reflects the adjusted mean change from baseline trajectory over the 18-month treatment period.

## 10.3 ANALYSIS DATASETS

Several analysis sets will be used in analyses:

- The main population for efficacy will be the modified intention-to-treat population (m-ITT), defined as all participants randomized, receiving at least one dose of study medication, and having at least one post-baseline efficacy assessment. Subjects will be analyzed by assigned treatment.
- A second analysis set will be used to assess the robustness of the primary and key secondary conclusions in the subset of participants in the m-ITT analysis set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effect of treatment according to the underlying scientific model. The Per Protocol (PP) analysis set will consist of all subjects in the m-ITT population who do not have a major protocol violation, inclusive of violation of entry criteria.
- The Safety Population is defined as all participants who are randomized and receive at least one dose of the study medication. The Safety Population will be used for all safety analyses. Subjects will be analyzed by assigned treatment.

## 10.4 DESCRIPTION OF STATISTICAL METHODS

### 10.4.1 General Approach

The design of this randomized controlled study is a parallel-group, two treatment, placebo-controlled investigation of pirfenodine vs placebo in participants receiving mycophenolate. Continuous variables will be summarized using descriptive statistics including n, mean, median, standard deviation, range (e.g., minimum and maximum). Qualitative variables will be summarized using counts and percentages. Summaries will be provided by treatment group and overall. Unless otherwise specified, statistical analyses will be performed using SAS Version 9 or higher. Where appropriate, statistical tests will be conducted at the 0.05 significance level using two-tailed tests and p-values will be reported.

### 10.4.2 Analysis of the Primary Efficacy Endpoint

The primary endpoint is change from baseline in the mean forced vital capacity, measured as the percentage of the age-, height-, gender- and race-adjusted predicted value (FVC-%) over the course of the 18-month treatment period, as reported quarterly (i.e., months 3, 6, 9, 12, 15 and 18). Given that the trajectories of the primary endpoint are expected to differ because of the mechanisms of action of the two treatment modalities, a longitudinal approach incorporating all time points will be employed. Specifically, the endpoint will be analyzed using a linear mixed model with participant-month in the study (3, 6, 9, 12, 15, 18) as the unit of analysis and the change from baseline in FVC-% as the outcome, with terms for baseline FVC-%, treatment group, month, the interaction of month (x) treatment group, and prior MMF therapy (stratification factor: naïve, >0 to $\leq$3 months, and >3 months to 6 months), as fixed covariates. Study participant will be treated as a random effect to account for the correlation of outcomes over time within a participant. The model generates adjusted estimates of change from baseline in the FVC-% for each treatment group and month, and an F-test will be used to test the hypothesis that the mean change from baseline during the treatment period differs between the two treatment groups. The model-based adjusted mean change from baseline in FVC-% will be presented graphically by treatment group by study month, with 95% confidence intervals (CIs) provided at each month.

The primary analysis of the primary efficacy endpoint will use the m-ITT analysis set. Appropriate non-linear parametric or non-parametric tests may be applied if the assumptions of the model are not satisfied. Details will be presented in the SAP.

To assess the robustness of treatment effects, a secondary analysis of the primary efficacy endpoint will be performed using the PP analysis set. In addition, two separate *a priori* analyses will be conducted using the model described above with the m-ITT analysis set: one with baseline CT fibrosis scores as a covariate, and one with baseline mRSS as a covariate.

Sensitivity analyses will be performed to assess how subjects who withdrew may affect conclusions of the analysis. In particular, our primary analytic approach assumes a missing-at-random mechanism (45) and one sensitivity analysis will employ a nonignorable model. With nonignorable missingness, the stochastic process that generates missingness is explicitly modeled. We will jointly model the longitudinal measures with the missing data mechanism using a pattern mixture model (31). Depending on the extent and pattern of missingness, other simpler sensitivity analyses may be used: for example, change from baseline to the end of treatment for subjects completing the study

(completers) may be analyzed using an analysis of variance model. The model will include the same covariates that are included in the primary mixed effects analysis.

In addition to the assessment of the overall trajectory of pulmonary response which integrates the timing of the onset of response and the overall magnitude of effect at 18 months, we will evaluate the individual components of this response. Using the same model as for the primary endpoint, we will assess the change point for response to evaluate the onset of response for the two treatment groups, and the change from baseline to month 18 to evaluate the overall magnitude of effect at the end of the treatment period.

In addition, frequency distributions of changes from baseline to 18 months in FVC-% will be presented by treatment group to describe observed (i.e., not model-based) estimates of treatment effects for the m-ITT analysis set, for those who completed 18 months of treatment and those who prematurely discontinued treatment. Additional analyses may be performed to assess more granular changes in treatment adherence (e.g., premature discontinuation of study treatment prior to 3, 6, 9, 12, 15 and 18 months) depending upon the observed extent and timing of discontinuation.

### 10.4.3 Analysis of the Secondary Endpoints and Exploratory Outcomes

#### 10.4.3.1 **Analyses of Secondary Endpoints.**

There are three categories of secondary outcomes:

1. Continuous outcomes such as change from baseline in mRSS, QLF-max and QILD-lung from HRCT, hemoglobin-adjusted DLCOHb-%, PROs, and compliance with pill administration during the treatment period;
2. Dichotomous outcomes such as the proportion of subjects who report improvement on the TDI at 18 months during the treatment period.
3. Time (in months) required for each treatment arm to achieve a 3.0% or greater improvement from baseline in the FVC-% over the 18-month treatment period.

Continuous secondary outcomes will be compared between treatment groups using the same methods as described for the primary analysis of the primary endpoint. For dichotomous secondary outcomes, logistic or Poisson regression will be used with treatment group, site, and prior MMF therapy (stratification factor: naïve, >0 to $\leq$3 months and >3 months to 6 months) included as covariates. For these dichotomous models, odds ratios (for logistic models) or relative risks (for Poisson models), with corresponding 95% CIs, will be presented; p-values for the test of treatment differences will also be presented. For time to event outcomes, Kaplan-Meier methods will be used to graphically present treatment differences; median time to event with 95% CIs and stratified (by prior MMF therapy) log-rank test p-values will be presented. The m-ITT analysis set will be used in the analyses of secondary endpoints.

In addition, the graphical descriptive approach described above to summarize the frequency distributions of changes from baseline to 18 months will be provided for key secondary endpoints (to be detailed in the SAP).

#### 10.4.3.2 **Analyses of Exploratory Outcomes.**

Comparable methods as described above for primary and secondary outcomes will be used for the exploratory aims described in Section 4.2.3. For example, identification of baseline features that predicted treatment responsiveness, disease progression and course of lung and skin

disease over time will employ the appropriate models with the baseline covariate and potentially the interaction of treatment and baseline as covariates. Separate models would be assessed for each outcome and baseline. Biomarker identification would be handled similarly. The identification of composite outcome measures that distinguish early and late treatment responses will be detailed in the SAP. These analyses will be considered exploratory and hypothesis-generating.

### 10.4.4 Safety Analyses

Safety analyses will be performed on the Safety analysis set. Safety data, including frequency of events and proportion of participants experiencing events described in section 8.1, clinical laboratory tests, vital signs, and physical examinations, will be summarized descriptively overall and by treatment group. For categorical safety outcomes, numbers and percentages will be used. For continuous safety outcomes, number, mean, standard deviation, median, interquartile range, minimum and maximum will be used to summarize changes from baseline to each study visit in laboratory tests and vital signs. Percent change from baseline will be added for laboratory values as outlined in the SAP. The primary organ system associated with each adverse event will be coded by the medical monitor. Kaplan-Meier methods will be used to summarize graphically the time to treatment failure, treatment emergent AEs and SAEs that result in discontinuation of treatment, and death.

### 10.4.5 Adherence & Retention Analyses

Participant disposition will be summarized descriptively. The number and percentage of participants randomized, completed, and withdrawing, along with reasons for withdrawal, will be tabulated overall, and by treatment group. The number of participants in each analysis population will be reported. Other disposition and study conduct information, including major protocol violations will be summarized. Duration of the study follow-up will be summarized overall and by treatment group.

Compliance with study medication will be assessed and summarized, including the proportion of participants who adhered to study treatment at each study visit, the median duration of adherence to study treatment and the proportion of participants who permanently discontinued study medication by reason for treatment permanent discontinuation, overall and by treatment group.

### 10.4.6 Baseline Descriptive Statistics

Prior to analysis, the two treatment groups will be compared descriptively with respect to demographic and baseline variables (e.g., age, race, FVC-%, mRSS). No statistical tests will be used to compare the treatment groups.

### 10.4.7 Planned Interim Analyses

#### 10.4.7.1 Safety Review

Safety outcomes will be presented at each DSMB meeting. These include number of and proportion of subjects with SAEs (including segregation of those involving deaths), treatment-emergent AEs, AEs of Special Interest, discontinuation of study medication due to AEs, and

protocol-defined treatment failures. These presentations will be descriptive, with no formal inferential methods used. Given that these study medications have been approved for other indications, their safety profile has been well characterized. Thus, no specific rules for halting study enrollment or study interventions for safety are specified; however, the DSMB may request formal inferential testing to assess the risk-benefit profile of these study medications in this study population.

10.4.7.2 **Efficacy Review**

No interim analysis is planned.

### 10.4.8 Additional Sub-Group Analyses

No other sub-group analyses (other than those described above for the primary and secondary efficacy endpoints) are planned.

### 10.4.9 Multiple Comparison/Multiplicity Analyses

No adjustments for multiplicity are planned since there is one primary analysis of the primary endpoint at the end of the study. Secondary analyses of the primary endpoint and analyses of the secondary endpoints serve to assess the robustness of the results and consistency of treatment effect on clinical outcomes important in this disease.

### 10.4.10 Tabulation of Individual Response Data

SAEs, deaths, and AEs resulting in discontinuation of study medication will be tabulated for participants who experience these events.

### 10.4.11 Exploratory Analyses

Additional analyses may be performed to explore both safety and efficacy measures collected in this study. The precise methods and analyses will be determined after the database is locked and the blind is broken. Thus all such analyses will be interpreted cautiously and not used for formal inference, although inferential statistics may be used as part of the data summary.

## 10.5 SAMPLE SIZE

### 10.5.1 Introduction & Background to Sample Size Determination

An initial sample size target of 150 participants (up to 190 consented and screened subjects to achieve 75 randomized per treatment group) was identified based on recent clinical trial experience and logistical considerations including the number of clinical centers with appropriate leadership and infrastructure to be considered as state of the art for treating SSc-ILD. Statistical analysis, using a clinical trials simulation approach, was then employed to estimate the power to detect various treatment effects on the primary endpoint with a two-sided Type I error of 5% and an 18-month attrition estimate of 24%.

Data from the SLS I and II clinical trials (44,50-52) were used to estimate the baseline characteristics of the proposed study population and their response over time to treatment with MMF, including the impact of prior treatment with MMF (occurring prior to study randomization), on the predicted

course of lung function changes over time. Note that SLS III will employ essentially the same patient recruiting centers and investigators as those that participated in the prior studies (with some new additions) and that the enrollment criteria have been relatively conserved over time to assure reproducibility. Furthermore, both the control arm and experimental arm of the proposed study will be treated with a course of cytotoxic therapy that is essentially identical to that reported from the SLS I and II studies. For the impact of PFD, safety and tolerability data from the LOTUSS trial (20) and outcome data from studies in which PFD was used to treat IPF (12-13) were considered informative.

### 10.5.2 Assumptions

Based on these available data, the following assumptions were used to generate clinical outcome scenarios for the potential response of FVC-% over time for both the control arm (MMF+Plac) and the experimental arm (MMF+PFD) of SLS III:

1) Data from SLS I and II were used as the best available data to estimate the standard deviation of the FVC-% values at different times in the study and the mean change in FVC-% at 3, 6, 9, 12, 15 and 18 months were assumed to follow a multivariate normal distribution, with equivalent variances in the two treatment groups.

2) In the same manner, data from the II study was used to inform the estimated impact of prior therapy with MMF, occurring prior to randomization, on the expected mean change in FVC-% and the variance of the FVC-% values at different times after randomization.

3) We measured the correlation structure over time for repeated measurement of the FVC-% in individual subjects participating in the SLS I study and applied that to the prediction of outcomes for SLS III. As one might assume, correlation between measurements taken at closer intervals is greater than measurements taken farther apart and from SLS I data the correlations among outcomes 3 months apart was 0.866, 6 months apart was 0.834, and 9 months apart was 0.802.

4) Treatment with cytotoxic therapy (MMF or CYC) is associated with an initial period of deteriorating lung function during the first 3-6 months of treatment that appears due to the required titration of cytotoxic medication over several months and the relatively slow clearing of existing immune mediators that drive inflammation and tissue destruction. This initial loss of lung function can average from -0.25% to -2.5%.

5) After an initial 3-6 month period that is associated with a relative decline of lung function, continued treatment with cytotoxic therapy is associated with a relative improvement in lung function over time that ranges from approximately +2.0 to +3.0% at 12 months and from approximately +3.0 to +5.0% at 18 months.

6) These time-dependent treatment response features, with an initial decline and delayed improvement, have a direct impact on the predicted course of the FVC-% over time in subjects who present to the study after several months of prior MMF therapy. The percentage of patients on cytotoxic therapy prior to randomization, and the length of prior treatment, need to be accounted for in predicting the overall course and magnitude of the change in FVC-% over time.

7) In contrast to the delayed effects of MMF, use of PFD for the treatment of IPF is associated with a rapid onset that slows the decline in lung function and is seen as early as 3 months.

8) In addition, given that the mechanisms of action for MMF and PFD are fundamentally different, it is reasonable to speculate that combination therapy (MMF+PFD) will have an overall impact on lung function at 18 months that is superior to either agent alone.

### 10.5.3 Defining the Primary Study Outcome

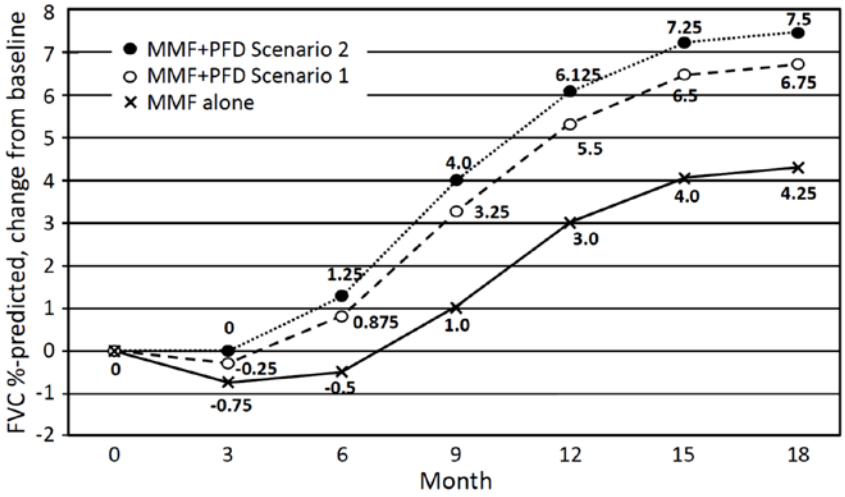
The primary aim of the study is to compare the impact of combining PFD and MMF in the experimental arm with that of MMF plus Plac in the control arm on pulmonary function during the 18-month double-blind period. The primary endpoint is change from baseline in the mean forced vital capacity, measured as the percentage of the age-, height-, gender- and race-adjusted predicted value (FVC-%) over the course of the 18-month double-blind treatment period. FVC is measured at baseline (pre-treatment) and then quarterly after treatment begins during the treatment period (i.e., months 3, 6, 9, 12, 15 and 18). Participants are required to have FVC-% ≤ 85% at screening.

### 10.5.4 Clinical Trial Scenarios and Simulations to Estimate Study Power in Treatment Naïve Patients

Two outcome scenarios were considered based on the two potential mechanisms of action by which the addition of PFD might improve the response to treatment with MMF alone. Both scenarios assume that the average response pattern to MMF alone (the control arm) would approximate the average response pattern to cytotoxic therapy observed from SLS II. In that study, the overall improvement from baseline in the FVC-% was approximately 3.0% at the 12 month time point and 4.25% at 18 months. Two different response scenarios were then proposed to represent the range of possible responses in patients treated with combined MMF+PFD (the experimental arm).

- ***In Scenario 1***, it is assumed that treatment with PFD is associated with an early slowing of the decline in lung function normally observed during the first 3-6 months of cytotoxic therapy and that there is only a small additive effect of PFD to the later improvement in lung function. The collective result is a 2.5% greater response to treatment at 12 months in the experimental versus control arms and this difference between the groups remains the same for the duration of the 18-month study.
- ***In Scenario 2***, it is assumed that treatment with PFD is associated with both an early slowing of the decline in lung function and a definite additive effect on the overall improvement in FVC-% that continues throughout the entire treatment period. The collective result is a 3.125% greater response to treatment at 12 months in the experimental versus control arms which continues to slowly increase to a final 3.25% difference between the two groups at 18 months.

**Figure 10.5.4. Hypothesized Response Trajectories over the 18-Month Double-Blind Treatment Period by Treatment Group with two scenarios considered, all participants naïve to therapy.**




The power to detect a response based on each Scenario was then calculated by carrying out 1,000 clinical trials simulations for each scenario in SAS 9.4, using a linear mixed model with participant-month in the study (3, 6, 9, 12, 15 and 18) as the unit of analysis and the change from baseline in FVC-% as the outcome, with terms for treatment group, baseline FVC-%, month and the interaction of treatment group with month as a fixed covariate and participant as a random effect to account for the correlation of outcomes over time within a participant. (This is a simplification of the model used for the primary analysis of the primary endpoint described above.) We used a compound symmetry variance-covariance structure. The average power is calculated as the number of simulations where the F-test used to test the hypothesis that the mean change from baseline during the double-blind treatment period differs between the two treatment groups is rejected ($p \leq 0.05$) divided by the number of simulations. 95% CIs for power are calculated based on the exact binomial proportion.

**Table 10.5.4.** Power to detect differences in the response pattern from baseline to 18 months for the primary outcome (change in FVC-%) when comparing the course of change in lung function over time for the MMF+PFD arm and the MMF+Plac arm according to the two proposed outcome scenarios. Results assume a 5% two-sided type I error and are provided for three different sample sizes (N = 75/arm; 70/arm and 65/arm)

**Assumptions:**

- Drop-out rates, variances and data inter-correlations presented below are derived from SLS I and II data and assumed to be identical for the two defined scenarios
- A 5% two-sided type I error is assumed
- The difference in the outcome measure between treatment arms (relative difference in the change from baseline in absolute FVC %-predicted) for each scenario was estimated based on the hypothetical response to PFD proposed for each scenario as detailed in **Figure 10.5.4**.

| **Scenario 1** Difference between treatment arms (FVC-%) | **Scenario 2** Difference between treatment arms (FVC-%) | **Dropout (Cumulative %)** | **SD Estimate** | **Assumed Correlations (AR1):** |
|---|---|---|---|---|
| Mo 3: 0.5 | Mo 3: 0.75 | Mo 3: 6.5% | Mo 3: 4.1 | 3-mo intervals: 0.866 |
| Mo 6: 1.375 | Mo 6: 1.75 | Mo 6: 13% | Mo 6: 5.1 | 6-mo intervals: 0.834 |
| Mo 9: 2.25 | Mo 9: 3.0 | Mo 9: 17% | Mo 9: 6.2 | 9-mo intervals: 0.802 |
| Mo 12: 2.5 | Mo 12: 3.125 | Mo 12: 20% | Mo 12: 6.9 | 12-mo intervals: 0.790 |

| | | | | |
|---|---|---|---|---|
| Mo 15: 2.5<br>Mo 18: 2.5 | Mo 15: 3.25<br>Mo 18: 3.25 | Mo 15: 23%<br>Mo 18: 24% | Mo 15: 6.2<br>Mo 18: 6.2 | 15-mo intervals: 0.780 |

**Power Calculations Scenario 1:**
Evaluation of Statistical Power by sample size, adjusting for drop outs over time, based on 1000 clinical trial outcome simulations:

| N per arm at baseline | N per arm at 18 mo | Estimated Statistical Power | 95% Lower Bound of Statistical Power | 95% Upper Bound of Statistical Power |
|---|---|---|---|---|
| 75 | 57 | 82.3% | 79.8% | 84.6% |
| 70 | 53 | 78.6% | 75.9% | 81.1% |
| 65 | 49 | 76.3% | 73.5% | 78.9% |

**Power Calculations Scenario 2:**
Evaluation of Statistical Power by sample size, adjusting for drop outs over time, based on 1000 clinical trial outcome simulations:

| N per arm at baseline | N per arm at 18 mo | Estimated Statistical Power | 95% Lower Bound of Statistical Power | 95% Upper Bound of Statistical Power |
|---|---|---|---|---|
| 75 | 57 | 95.6% | 94.1% | 96.8% |
| 70 | 53 | 92.6% | 90.8% | 94.2% |
| 65 | 49 | 91.8% | 89.9% | 93.4% |

Note that with the given m-ITT design, the linear mixed effects model will actually include data from all subjects who have at least a baseline and one follow-up measure of FVC-%. In this setting, even with an overall 24% attrition by the end of 18 months, it is estimated that 83% of the maximal possible study outcome data points (assuming no attrition) would be included in the analysis.

According to Scenario 1, which is strictly based on the documented capacity for PFD to slow the rate of decline of lung function in patients with IPF who are not receiving any other treatment, a sample size of 75 patients per treatment arm is required to obtain a minimum power of 80% (i.e., 80% is within the 95% CI for this prediction). If PFD has novel effects when combined with MMF so that it both reduces the rate of lung decline and works in concert with MMF to improve overall lung function (i.e., Scenario 2), then the predicted outcome will be much more reliably detected and a smaller sample size would be sufficient.

### 10.5.5 Impact of a Mixed Population of Treatment Naïve and Previously-treated Patients on the Estimate of Study Power

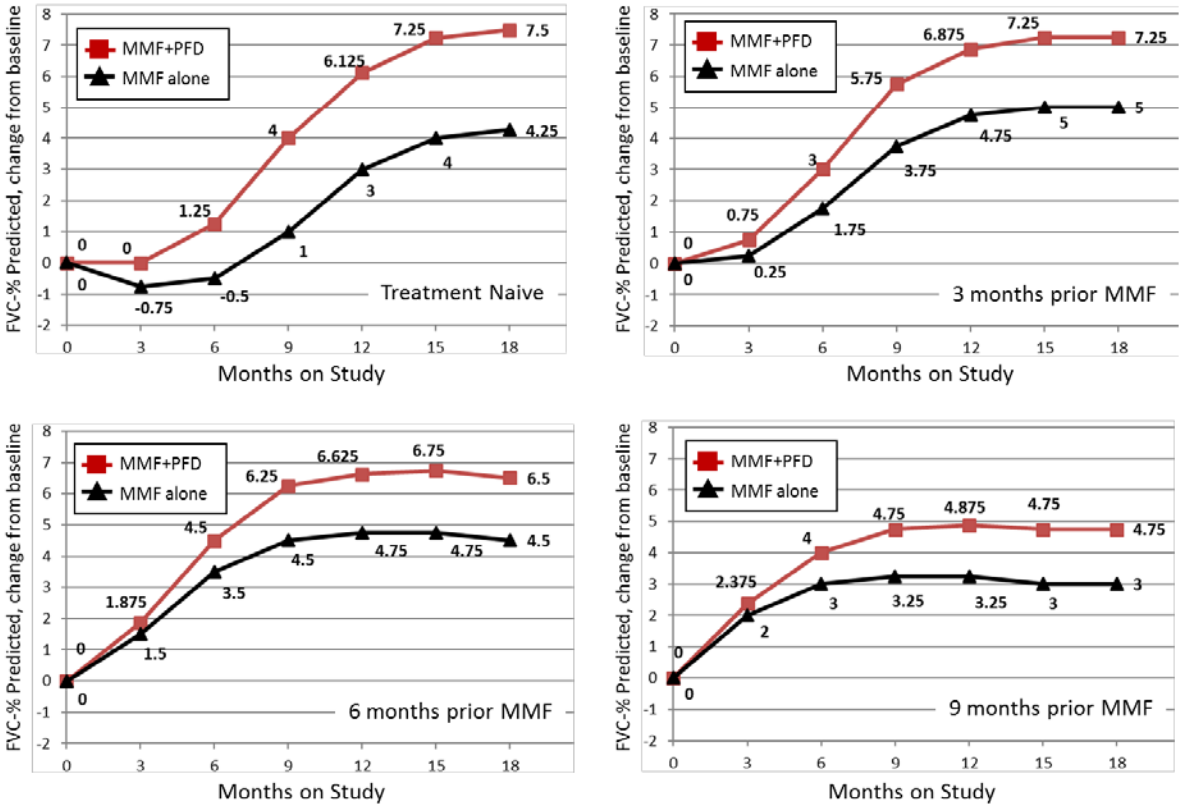
Having established adequate estimates of study power in a population of treatment naïve patients, the clinical trial Scenarios were then adjusted to assess the impact of a mixed starting population of patients in which some of the participants are treatment naïve and others have been on prior treatment with MMF (or DMARD with similar activity) for a period of 3, 6 or 9 months. Additional assumptions associated with these modified Scenarios include:

1) The mean change in FVC-% over a given 3-month interval and the corresponding impact on the standard deviation of the FVC-% measurement will always reflect the total time that a patient has been on therapy, including therapy that was administered before randomization and therapy that was administered following randomization.

2) The treatment effect is measured as the change from baseline, in which baseline is determined at the time of randomization (baseline visit). The baseline FVC-% measurement therefore establishes the zero reference value for evaluating change over time in response to the time that a patient is on the protocol. In this setting, patients who have been on 3 months or more of MMF will not be expected to experience the initial decline in lung function that occurs when enrolling treatment naïve patients.

3) As one of the hypothesized benefits of starting PFD and MMF at the same time in treatment naïve patients is the prevention of an early decline in lung function, there is a relative treatment penalty in the predicted PFD+MMF arm when patients have been on prior therapy with MMF. This results in less and less separation between the course of the two treatment arms as the length of time on prior MMF increases. This impact must be accounted for when modeling treatment outcomes and predicting study power.

**Figure 10.5.5. Hypothesized Response Trajectories over the 18-Month Double-Blind Treatment Period by Treatment Group for Scenario 2 based on length of time on MMF therapy prior to randomization.**




The power to detect a response according to Scenario 2, when taking into account the length of prior treatment with MMF (naïve, 3 mo, 6 mo and 9 mo strata) and the percentage of subjects within each of these strata, was then calculated by carrying out 1,000 clinical trials simulations for each situation in SAS 9.4 as already described. We varied the proportion of patients from 100% naïve down to 50% naïve, with the distribution across the prior treatment with MMF strata varied as described below. Estimates of the differences between treatment arms and the standard deviation

for the measurements at a given time were adjusted according to the scenario curves shown in Figure 10.5.5.

**Table 10.5.5.** Power to detect differences in the response pattern from baseline to 18 months for the primary outcome (change in FVC-%) when comparing the course of change in lung function over time for the MMF+PFD arm and the MMF+Plac arm according to Scenario 2 with different mixtures of treatment naïve patients and those who were on prior MMF therapy for 3, 6 or 9 months as indicated. Results assume a 5% two-sided type I error and are provided for three different sample sizes (N = 75/arm; 70/arm and 65/arm)

**a. Scenario 2: N = 75 per arm**

| % per stratum (length of prior MMF) | | | | Estimated statistical power based on 1000 clinical trial outcome simulations | | |
|---|---|---|---|---|---|---|
| **Naive** | **3 mo** | **6 mo** | **9 mo** | **Power** | **95% Lower Bound** | **95% Upper Bound** |
| 1.00 | 0.00 | | | **95.6%** | 94.1% | 96.8% |
| 0.80 | 0.20 | | | **93.8%** | 92.1% | 95.2% |
| 0.75 | 0.25 | | | **92.2%** | 90.4% | 93.8% |
| 0.70 | 0.30 | | | **90.8%** | 88.8% | 92.5% |
| 0.60 | 0.40 | | | **90.5%** | 88.5% | 92.2% |
| 0.50 | 0.50 | | | **86.1%** | 83.8% | 88.2% |
| 0.80 | 0.10 | 0.10 | | **91.4%** | 89.5% | 93.1% |
| 0.70 | 0.20 | 0.10 | | **89.5%** | 87.4% | 91.3% |
| 0.70 | 0.10 | 0.20 | | **90.2%** | 88.2% | 92.0% |
| 0.60 | 0.30 | 0.10 | | **89.0%** | 86.9% | 90.9% |
| 0.60 | 0.20 | 0.20 | | **88.2%** | 86.0% | 90.1% |
| 0.60 | 0.10 | 0.30 | | **85.2%** | 82.8% | 87.3% |
| 0.50 | 0.40 | 0.10 | | **84.7%** | 82.3% | 86.9% |
| 0.50 | 0.30 | 0.20 | | **82.7%** | 80.2% | 85.0% |
| 0.50 | 0.20 | 0.30 | | **82.7%** | 80.2% | 85.0% |
| 0.50 | 0.10 | 0.40 | | **79.7%** | 77.1% | 82.2% |
| 0.70 | 0.10 | 0.10 | 0.10 | **86.4%** | 84.1% | 88.5% |
| 0.60 | 0.20 | 0.10 | 0.10 | **86.2%** | 83.9% | 88.3% |
| 0.60 | 0.10 | 0.20 | 0.10 | **83.7%** | 81.3% | 85.9% |
| 0.50 | 0.30 | 0.10 | 0.10 | **79.9%** | 77.3% | 82.3% |
| 0.50 | 0.20 | 0.20 | 0.10 | **79.3%** | 76.7% | 81.8% |

**b. Scenario 2: N = 70 per arm**

| % per stratum (length of prior MMF) | | | | Estimated statistical power based on 1000 clinical trial outcome simulations | | |
|---|---|---|---|---|---|---|
| **Naive** | **3 mo** | **6 mo** | **9 mo** | **Power** | **95% Lower Bound** | **95% Upper Bound** |
| 1.00 | 0.00 | | | **91.8%** | 89.9% | 93.4% |
| 0.80 | 0.20 | | | **91.3%** | 89.4% | 93.0% |
| 0.70 | 0.30 | | | **88.1%** | 85.9% | 90.0% |
| 0.60 | 0.40 | | | **86.0%** | 83.7% | 88.1% |
| 0.50 | 0.50 | | | **84.6%** | 82.2% | 86.8% |
| 0.80 | 0.10 | 0.10 | | **89.4%** | 87.3% | 91.2% |
| 0.70 | 0.20 | 0.10 | | **88.7%** | 86.6% | 90.6% |
| 0.70 | 0.10 | 0.20 | | **85.6%** | 83.3% | 87.7% |
| 0.60 | 0.30 | 0.10 | | **85.7%** | 83.4% | 87.8% |
| 0.60 | 0.20 | 0.20 | | **82.9%** | 80.4% | 85.2% |
| 0.60 | 0.10 | 0.30 | | **81.5%** | 79.0% | 83.9% |
| 0.50 | 0.40 | 0.10 | | **83.0%** | 80.5% | 85.3% |
| 0.50 | 0.30 | 0.20 | | **81.5%** | 79.0% | 83.9% |
| 0.50 | 0.20 | 0.30 | | **79.9%** | 77.3% | 82.3% |
| 0.50 | 0.10 | 0.40 | | **79.9%** | 77.3% | 82.3% |

**c. Scenario 2: N = 65 per arm**

| % per stratum (length of prior MMF) | | | | Estimated statistical power based on 1000 clinical trial outcome simulations | | |
|---|---|---|---|---|---|---|
| **Naive** | **3 mo** | **6 mo** | **9 mo** | **Power** | **95% Lower Bound** | **95% Upper Bound** |
| 1.00 | 0.00 | | | **91.8%** | 89.9% | 93.4% |
| 0.80 | 0.20 | | | **88.2%** | 86.0% | 90.1% |
| 0.70 | 0.30 | | | **85.5%** | 83.2% | 87.6% |
| 0.60 | 0.40 | | | **81.4%** | 78.9% | 83.8% |
| 0.50 | 0.50 | | | **79.7%** | 77.1% | 82.2% |
| 0.80 | 0.10 | 0.10 | | **87.1%** | 84.9% | 89.1% |
| 0.70 | 0.20 | 0.10 | | **85.5%** | 83.2% | 87.6% |
| 0.70 | 0.10 | 0.20 | | **83.2%** | 80.7% | 85.5% |
| 0.60 | 0.30 | 0.10 | | **78.4%** | 75.7% | 80.9% |
| 0.60 | 0.20 | 0.20 | | **77.5%** | 74.8% | 80.0% |

According to these predictions for Clinical Trial Scenario 2, representing the primary outcome to be investigated, the study is adequately powered (80% power or greater) to detect a difference between the two treatment arms when the sample size is 150 and the patient population contains at least 50% treatment naïve patients. If the remaining 50% of enrolled patients are limited to no more

than 6 months of prior therapy with MMF, then adequate power is maintained across the entire range of anticipated distributions between subjects with up to 3 mo of prior therapy and those with between 3 to 6 mo of prior therapy.

As a result, the target study population will consist of at least 50% of patients who are treatment naïve and up to 50% of patients who recently started on therapy within 6 months of entering the study (as detailed in Table 10.5.5 above). With this mixture of patients, the power remains adequate even if only 70 patients are enrolled in each arm (total randomization 140 patients), providing optimal flexibility for the enrollment phase of the study.

When a similar statistical approach is applied to Clinical Trial Scenario 1, in which only a small additive effect of PFD is modeled in addition the the underlying treatment response to MMF, the power to detect a difference between the two treatment arms is adequate (80% power or greater) when the sample size is 150 and the patient population contains at least 75% treatment naïve patients. When the percentage of treatment naïve patients is reduced to 50%, the predicted power is at best 75% (assumes % per stratum of 50% naïve, 40% 3 mo, 10% 6 mo).

## 10.6 MEASURES TO MINIMIZE BIAS

### 10.6.1 Enrollment/Randomization/Masking Procedures

This study will use randomization and masking as two of the cardinal principles of clinical trials to minimize bias.

*Randomization.* Participants will be randomized after all screening assessments have been completed and the investigator has verified that eligibility criteria have been met. At the time of randomization, participants will be assigned a unique randomization number; no participant may begin treatment prior to randomization. Eligible participants will be randomized to PFD+MMF or MMF+Plac in a 1:1 manner, stratified by clinical site (pooled into 4 groups) and prior MMF exposure (naïve, >0 to $\leq$3 months, and >3 months to $\leq$6 months). Randomization to the different strata will be capped if necessary to maintain at least 50% of randomized subjects within the treatment naïve strata (no prior therapy with MMF or DMARD) in order to maintain adequate power (as detailed in Section 10.5). The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the coordinators to enter participant information (e.g., participant ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the site pharmacists. Participants who withdraw from the study prior to completion of the treatment period will not be replaced.

*Blinding.* This is a double-blind study. The study staff (except for select staff at the Data Coordinating Center and Research Pharmacists) and the participant are blinded to the treatment assignment.

### 10.6.2 Evaluation of Success of Blinding

Not applicable.

### 10.6.3 Breaking the Study Blind/Participant Code

Blinding is critical to the integrity of this clinical study. All participants will receive MMF in an open-label manner and blinding pertains only to their assignment to either PFD or matching placebo. There are two identified situations in which unblinding to identify the investigational drug will be considered.

#### 10.6.3.1 **Unblinding associated with protocol-defined Treatment Failure.**

As detailed in Section 5.3.2, subjects who meet criteria for a protocol-defined treatment failure will be withdrawn from both PFD/Plac and MFF (i.e., the active drug treatment phase of the trial) and their clinical management transfered to an identified treating physician at the discretion of the patient. The study blind will not be broken unless the treating physician is convinced that unblinding is required in order to appropriately treat the patient and their request is reviewed and agreed to as compelling by the Executive Committee.

#### 10.6.3.2 **Unblinding associated with emergent medical necessity.**

In addition, in the event of a medical emergency in which knowledge of the investigational product is deemed critical to the participant's management, the blind for that participant may be broken. Before breaking the blind of an individual participant's treatment, the investigator should have determined that the information is necessary, i.e., that it will alter the participant's immediate management. Unless time is of the essence due to the emergency nature of the participant's medical condition, any request for unblinding must be reviewed and agreed to as compelling by the Executive Committee. However, the investigator holds sole responsibility for the decision to unblind in case of emergency.

In many cases, particularly when the emergency is not investigational product-related, the problem may be properly managed by assuming that the participant is receiving active product without the need for unblinding. Should unblinding of a study participant be necessary because of an emergency, the site personnel will login to the password-protected electronic database application (developed and maintained by the DCC) that will provide the treatment assignment. Audit procedures will ensure that the name of the individual associated with the login will be communicated to the DCC. As an additional safety measure, the personnel at the clinical sites will be provided with telephone numbers to contact the DCC and/or Pharmacy personnel having access to the treatment assignment on a 24-7 basis. If unblinding occurs, it is the responsibility of the investigator to promptly document and explain any unblinding and the circumstances that led to it will be reviewed by the study Executive Committee.

## 11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Every participating clinical site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Participating clinical sites will also obtain institutional authorization for external monitoring by the Sponsor, Data Coordinating Center and the FDA to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are defined as all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant's memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes, recorded data from automated instruments, copies or

transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfildm x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents when the data is collected and recorded there as the primary source of information, but CRFs will not constitute the only form of source document information for this trial.

# 12 QUALITY ASSURANCE AND QUALITY CONTROL

DCC staff will prepare data management and clinical monitoring plans. The clinical monitoring plan will detail procedures to assess accuracy of the database relative to source documents, as well as site adherence to regulatory and study procedures. Emphasis will be placed on the process of consenting subjects, compliance with regulatory requirements and study protocol, values of key endpoints, and identification of SAEs that may not have been reported. The data management plan will describe the front-and back-end edit checks, as well as forms tracking procedures, that will be implemented to ensure timely and high-quality data collection. It will also define the periodic reports that will be shared with site coordinators and PIs that summarize site performance. The clinical monitoring and data management procedures will be consistent with the International Conference on Harmonisation (ICH E6) standards for Good Clinical Practice (GCPs).

Quality Assurance monitoring for essential study procedures and outcomes will be handled by the Core Programs including the Pulmonary Function Core, Radiology Core, Pharmacy Core and the Biorepository Core. These Core programs will prepare independent manuals of operation and assume responsibility to inventory and monitor quality features of every study performed. Core inventory and quality assurance reports will be prepared in advance of and included as a component of each DSMB review.

Monitoring of Protocol Compliance will be carried out as detailed in Section 9.0 on Clinical Monitoring under the direction of the DCC according to a defined Clinical Monitoring Plan. The Executive Committee will meet at least twice monthly to review site monitoring reports as they become available, enrollment and retention reports, interval AEs and SAEs, drug compliance, protocol compliance including interval study withdrawals and treatment failures, delinquincy reports, regulatory status updates, and interval reports from the Core Programs as available.

# 13 ETHICS/PROTECTION OF HUMAN SUBJECTS

## 13.1 ETHICAL STANDARD

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 codified 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 compliant with Federal HIPAA Guidelines.

## 13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form by the responsible IRB having jurisdiction over each clinical site form must be obtained before any

participant is enrolled at that site. Any amendment to the protocol will require review and approval by the IRB of record for each site before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

## 13.3 INFORMED CONSENT PROCESS

It is the responsibility of the named investigators at each participating clinical 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. The participant will sign the informed consent document prior to any procedures being done specifically for the study. 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 HIPAA 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.

## 13.4 SAMPLE INFORMED CONSENT LANGUAGE

---

**DAVID GEFFEN SCHOOL OF MEDICINE AT**
**THE UNIVERSITY OF CALIFORNIA LOS ANGELES**

**CONSENT TO PARTICIPATE IN RESEARCH**

| | |
|---|---|
| **StudyTitle:** | **Scleroderma Lung Study III (SLS 3):** Combining the anti-fibrotic effects of pirfenidone (PFD) with mycophenolate (MMF) for treating scleroderma-related interstitial lung disease |

**UCLA Site Principal Investigator:** S. Samuel Weigt, M.D.
**Coordinating Center Principal Investigator:** Michael D. Roth, M.D

**INTRODUCTION**

S. Samuel Weigt, M.D., who is the Principal Investigator responsible for the UCLA site and Michael D. Roth, M.D., who is the Principal Investigator for the overall research study, and their associates from the Pulmonary and Rheumatology Divisions of the Department of Medicine at the University of California, Los Angeles, are conducting a research study.

The researchers will explain this study to you. Research studies are voluntary and include only people who choose to take part. Please take your time about deciding whether to participate in this study. Before deciding:

- You can discuss this study with friends and family.
- You can also discuss it with your health care doctor or request a second opinion.
- If you have any questions, you can ask the researchers for more information before deciding to participate.

The research team is asking you to participate in this study because you are at least 18 years of age, have been diagnosed with Scleroderma (also called Systemic Sclerosis), your disease is felt to have been active for less than 7 years, and there are signs that you have lung involvement that includes shortness of breath and abnormal lung tests.

## WHY IS THIS STUDY BEING DONE?

This research will use a double-blinded design (meaning that neither you nor the treating doctors will know which treatment you are on) to compare the safety and effectiveness of two experimental drug treatments for Scleroderma-related lung disease. One treatment involves taking mycophenolate as the only study drug along with a placebo (a sugar capsule that looks the same as pirfenidone). The other treatment involves taking a combination of mycophenolate along with pirfenidone.

This research is designed to test whether combining pirfenidone and mycophenolate will result in a more rapid and possibly greater improvement in lung function than occurs when mycophenolate is used alone. While both of these drugs have been approved by the U.S. Food and Drug Administration (FDA) to treat other medical conditions, neither drug has been FDA-approved for the treatment of scleroderma-related lung disease.

This study is being funded in part by Genentech, Inc.

## HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

This study will enroll 150 patients with Scleroderma-related lung disease at research centers nationwide with the expectation that up to 20 will take part at the UCLA site.

## WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

### Before you begin the study: Screening

In order to determine if you are eligible for the study you will need to undergo a two-part screening process.

In the first part of the screening, a routine medical history and physical examination will be performed. You should bring medical records for review of your history as you would for any new medical evaluation. A blood sample will be drawn from your arm to check your blood counts, liver and kidney tests. If you recently completed blood tests (within the past 30 days) you should bring a copy of these results with you and, if they meet the requirements of the study, you may not need another blood draw. Unless already completed within the prior 30 days and considered to meet the needs of the study, you

will undergo breathing tests to measure how deep of a breath you can take, how easily you can blow out air from the lungs, and how well your lungs work at taking up gas into the bloodstream. A brief questionnaire detailing any gastrointestinal symptoms will be completed.

If you appear to qualify for the study based on the first stage of screening, then you will be asked to complete the second part of the screening and undergo a high resolution computerized x-ray examination of the lungs (chest HRCT scan). If you recently completed a chest HRCT scan (within the past 45 days) you should advise the study physician as it can be considered in place of completing another scan. If it is found to meet all of the required study criteria the study physician will advise you of this and a repeat chest HRCT scan performed specifically for the study will not be necessary. Otherwise, to complete this test you will lie still on a table that moves into a large donut-shaped machine and you will be asked to take a full deep breath and hold your breath at certain times. A computer will then provide us with very detailed images 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.

The final determination regarding whether you are eligible will not be made until you return for the first baseline visit.

**Before you begin the study: Washing-out other medications**

If you appear to qualify for the study based on results from the screening described above and you are currently (or within the past 30 days) taking either one of the study drugs (mycophenolate or pirfenidone) or another medication that might also act as a treatment for scleroderma-related lung disease (the research team will let you know), then you may need to stop these treatments and let their effects wash-out from your system. While a period of at 30 days off these medications is routinely recommended before randomization to one of the study treatment arms, the study physician will review the details related to your medical condition and help determine whether stopping the pre-study medication or continuing on it is recommended. The decision will be based on what is considered to be in your best interests after considering your history, lab findings and the potential risks and benefits.

**During the study:**

If you take part in this study, the researcher(s) will assign you to one of the treatment groups, ask you to undergo several procedures, and you will need to return for a number of study visits and procedures over the course of the next 19 months. The details are described below and a chart summarizing each procedure and each visit is included on the last page of this consent.

<u>Baseline Visit (Visit 1, Month 0)</u>

You will return to the clinic within 90 days of your first screening visit for Visit 1. 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 set of health questionnaires regarding your shortness of breath, your ability to function, how short of breath you are, symptoms of cough, and how you rate your quality of life in respect to scleroderma and your lung problems. These questionnaires will take 20-30 minutes to complete. You have the right to refuse to answer any question you do not wish to answer.
- You will also 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 similar to those performed during the screening.
- 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 will have a pregnancy test if you are a woman who is able to become pregnant.

If it is determined that you are eligible for the study, you will be randomly assigned to one of the study groups indicated below and given medication to take home with you. Because some test results may not be available immediately, the determination of eligibility might 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.

Treatment Group Assignment

If you qualify, you will be randomly assigned (like the flip of a coin) to one of the following two groups:
- Mycophenolate, up to a target dose of 1.5 gram twice daily, as tolerated, plus placebo capsules.
- Mycophenolate, up to a target dose of 1.5 gram twice daily, as tolerated, plus pirfenidone, administered up to a target dose of 801 mg three times daily 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 the dose for some participants. You have an equal (50/50) chance of being in either group. Some participants will receive placebo capsules instead of pirfenidone. A placebo is a pill that looks like the study drug but contains no active medication. The placebo 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 the target doses; rather your dose will be titrated up (slowly increased) to the indicated doses but it may be held or continued at a lower dose if you do not tolerate. People in the mycophenolate plus pirfenidone group will receive two active drugs without a placebo.

Regular Follow-up Visits (Visits 3, 5-9, 12, 15, 18, 21)

***Blood and Urine Testing***

There are a number of potential side effects of the study drugs that may be detected only through regular blood testing. Therefore, you will be required to attend a clinic to give regular blood (1 ½ - 3 ½ teaspoons) for routine lab tests and urine for pregnancy testing, if applicable, throughout the study. **These samples will be collected every month for the first 6 months and every 3 months thereafter**. Based on your tolerance of the medication and the results of this laboratory testing, your dosage of medication may be adjusted and it is possible that additional blood testing might be required to monitor more closely.

***Other Monitoring and Assessments***

During each of these regular follow-up visits you will also see a study doctor and the study staff so that other monitoring and outcome assessments can take place. Each assessment will not necessarily be completed at each visit, so the timing for each one is indicated below.

- You will review any changes in your health or medication with the study doctor, and answer questions about your symptoms.
  - This will occur at every visit (Visits 3, 5-9, 12, 15, 18, 21).
- You will have a targeted physical exam in order to assess the extent of your scleroderma.
  - This will occur at every visit (Visits 3, 5-9, 12, 15, 18, 21).
- You will be asked to maintain a study medication calendar and keep all of the bottles of study drugs that are supplied to you. You will need to bring the completed calendar and all bottles and containers of medication, whether completely or partially used (or not used at all) to every visit. A study coordinator will review the calendar and your use of medications at every visit.
  - These will be checked at every visit (Visits 3, 5-9, 12, 15, 18, 21).
- You will complete breathing tests to measure how deep of a breath you can take, how easily you can blow out air from the lungs, and how well your lungs work at taking up oxygen into the bloodstream.
  - This testing will occur at 3 month intervals (Visits 6, 9, 12, 15, 18, 21). Breathing tests will take approximately 30-45 minutes to complete.
- You will complete health-related questionnaires.
  - Questionnaires directly assessing your breathing and the impact of shortness of breath on your activity will need to be completed at 3 month intervals (Visits 6, 9, 12, 15, 18, 21). These questionnaires will take 10-20 minutes to complete. You have the right to refuse to answer any question you do not wish to answer.
  - Questionnaires regarding your ability to function, symptoms of cough, any gastrointestinal symptoms, and how you rate your quality of life in respect to your scleroderma will need to be completed at 6 month intervals (Visits 9, 15, 21). These questionnaires will take 10-20 minutes to complete. You have the right to refuse to answer any question you do not wish to answer.

<u>Interval Phone Visits (Visits 2, 4, 10-11, 13-14, 16-17, 19-20)</u>

Some of the regular monitoring for this study will occur over the phone and will not require that you present to the clinic (or study center) for an in-person visit. At a pre-arranged date and time, the study team will contact you to obtain information about how you are doing, ask you whether any changes to your health or use of medications has occurred, ask you to report any side effects or adverse health events, and to review the use of your study drugs.

<u>Extra Follow-up Safety Visits (if needed)</u>

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

<u>Visit 15 (Month 12 = 336 days, +/- 14 days)</u>

In addition to testing completed at the Regular Follow-up Visits described above, 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. This will be taken at the same time as your other blood sample and will not require an extra needle-stick.
- You will have a more extensive history and physical examination with the study physician

that will include an overall assessment of your health in addition to issues specifically related to Scleroderma and Scleroderma-related lung disease

Visit 21 (Month 18 = 504 days, +/- 14 days)

In addition to testing completed at the Regular Follow-up Visits described above, 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. This will be taken at the same time as your other blood sample and will not require an extra needle-stick.
- You will undergo a high resolution CT (HRCT) scan of the chest.

Final Follow-up Telephone Visit (Visit 22 or within 30 days of permanently stopping treatment if that should happen)

At a pre-arranged date and time, the study team will contact you to carry out the final study contact. This might occur one month after completing the entire 18 months of active drug treatment or it might occur within 30 days of permanently stopping treatment and prematurely withdrawing from the study, if that should occur. As part of this final telephone visit, the following will take place.

- You will review any changes in your health or use of medications and answer questions about your symptoms.
- You will be asked to report any side effects or adverse health events

**Additional Visit for those who prematurely discontinue taking the study treatment:**

If you prematurely and permanently stop taking study drugs for any reason (i.e. stop both pirfenidone/placebo and mycophenolate), you will be asked to return to the clinic for the Month 12 and Month 18 visits as described above. The additional visits and the data obtained from them will help achieve our research goals even if you are no longer taking study drug. While we ask that you return for the visits if at all possible, you have the right to refuse to complete the visits.

However, If only the pirfenidone/placebo study drug is permanently stopped, and you are approved to continue taking mycophenolate according to the protocol, then you may continue participation in all study visits according to the normal study protocol.

**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 drugs (both the pirfenidone/placebo capsules and the mycophenolate capsules.) 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 Month 12 and Monh 18 visits as detailed above. The additional visits and the data obtained from them will help achieve our research goals even if you are no longer taking study drug. While we ask that you return for the visits if at all possible, you have the right to refuse to complete the visits.

**HOW LONG WILL I BE IN THIS STUDY?**

This study will last approximately 19 months from the time you are assigned to a specific treatment group, which includes the 18 months of active drug therapy and the final telephone follow-up approximately 30 days after stopping drug therapy. Your participation is voluntary and if you should decide to do so, you may withdraw at any time in which case your participation would be shorter than described.

In addition to your participation in the study visits described above, you will be asked at the end of this consent form (section on "Signature of the Participant") to indicate whether you are willing (or not) to be contacted on an annual basis for up to 5 years after you complete this study. During this contact you will be asked to provide an update regarding your health, symptoms related to your scleroderma and to describe any other treatments that you might have received for your condition.

**WHAT KINDS OF RISKS OR DISCOMFORTS COULD I EXPECT?**

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. All drugs and testing have the potential for side effects. Although the experimental drug treatments that will be used in this study have been well- tested in laboratory and animal studies, and in patients taking them for other reasons, the potential side effects in patients with scleroderma are not completely known at this time. You will be followed closely by the study team for the entire time you are a part of this study. If you experience any side effects from the study, the researchers will provide you with the treatment that has the best chance of taking care of the side effects. If you experience any side effects related to the study drugs that continue at the end of study, we will continue to follow-up with you until these effects stabilize or resolve.

**Known risks and discomforts associated with the study drugs:**

<u>Risk of pregnancy and breast feeding during study treatment:</u>

Mycophenolate can harm the fetus when administered to a pregnant woman and use of mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss 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, kidney and nervous. There are no adequate and well-controlled studies of pirfenidone in pregnant women but it was not found to be harmful in animal studies. It is not known whether or not these drugs are excreted in human breast milk, but many drug are. In addition, there may also be other unknown risks of the study drugs and procedures to pregnant women, fetuses, and nursing children. As all study participants will receive mycophenolate, those 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 fallopian tubes, uterus and/or ovaries) and wish to participate will be required to use approved contraception methods and to be monitored with frequent urine pregnancy tests throughout the study. Women who are breastfeeding will not be eligible to participate in this study.

For this reason, women who are able to become pregnant must agree to either abstinence (to avoid heterosexual intercourse completely) or use <u>two acceptable methods</u> of birth control throughout the study and must have negative urine pregnancy tests in order to continue their participation in

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 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, the funding source (Genentech, Inc.) and with the IRB (Institutional Review Board).

Risks of Mycophenolate:

For the risks of the study drug noted below, the number in parentheses indicates the percentage of patients in whom the side effects have been seen.
***Common risks*** experienced by patients taking mycophenolate to prevent organ transplant rejection include:

- Urinary tract infection (37%)
- Diarrhea (31%), constipation (23%), and nausea (20%)
- Hypertension (28%)
- Peripheral edema (swelling of tissues, usually in the lower limbs, 29%)
- Anemia***** (low red blood cells, 26%), leucopenia (low white blood cells, 23%), and thrombocytopenia (low blood platelets, 10%)
  *****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.
- 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 intestine, 5%)

Like all drug treatments that suppresses the immune system, the use of mycophenolate can increase the risk of infections and it is important to use good hygiene, avoid obvious exposures to those with active infections, and to report any concerns about infection as early as possible to your primary doctor and the study team. Other side effects may be dose-dependent and this study will slowly increase the dose of mycophenolate over several months, monitor for any problems, and adjust the dosing if necessary to help avoid serious problems.

***Rare (infrequent) but serious risks*** experienced by patients taking mycophenolate to prevent organ transplant rejection include:

- Progressive multifocal leukoencephalopathy (PML) is a neurologic disorder that can be fatal and has been reported in patients that were taking mycophenolate. However, all of the patients receiving mycophenolate for prevention of transplant rejection in whom PML has been reported were receiving other drugs that cause severe immunosuppression at the same time and PML has not previously been reported in patients treated with mycophenolate as the sole immunosuppressive drug.

- BK Virus has been rarely reported when mycophenolate is used in combination with other drugs that cause immunosuppression. A large portion of the general population already carries BK Virus with no symptoms, but taking mycophenolate may cause you to develop symptoms, like kidney problems. In general, reactivation of latent (resting) viruses is a theoretical risk whenever the immune system has been severely depressed by drugs.
- Pure red cell aplasia (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. Cases of PRCA have been reported in patients treated with mycophenolate when used in combination with other drugs that suppress the immune system. PRCA has not previously been reported in patients treated with mycophenolate as the sole immunosuppressive drug for scleroderma-related lung disease.
- Patients receiving immunosuppression that involves a combinations of drugs, including mycophenolate as part of the treatment, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the specific use of mycophenolate. As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients when they were receiving mycophenolate (2 g or 3 g daily) along with other immunosuppression as part of the treatment for kidney, heart, and liver transplantation. Lymphoma has not previously been reported in patients treated with mycophenolate as the sole immunosuppressive drug for scleroderma-related lung disease, although there have been reports of benign skin cancer.

Most of the patients in whom the rare but serious side effects noted above were seen were also receiving other drugs known to cause immune suppression and to be associated with these complications. Few serious side effects have been reported in patients receiving mycophenolate for scleroderma-related lung disease and this study has been specifically designed to avoid the use of other potent immune suppressive drugs.

Risks of Pirfenidone:

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

***Common risks*** experienced by patients taking pirfenidone to treat idiopathic pulmonary fibrosis include:

- Skin rashes (30%), photosensitivity skin reactions (those occurring in sun-exposed skin; 9%), and itching (8%)
- Nausea (36%), Diarrhea (26%), Abdominal discomfort (which can include stomach, upper abdomen or lower abdomen; 22%), Indigestion (19%), Vomiting (13%), and gastroesophageal reflux (the feeling that acid is backing up into the esophagus; 11 %),
- Fatigue (26%)
- Dizziness (18%), altered taste (6%), Insomnia (10%)
- Decreased appetite (13%), Weight loss (10%)
- Achy joints (10%)
- Elevation of liver enzymes (ALT, AST, GGT, 0.3% - 4% each)

In most cases (>80%), the common side effects associated with taking pirfenidone are only mild to moderate in severity, occur more frequently when first starting the drug treatment and often

resolve with time, and are dose-dependent. Skin rashes that occur in sun-exposed skin can be avoided by wearing hats, long sleeves, and using sunscreen whenever you are going to be out in the sun. If skin rashes do develop, the most often respond to a simple over the counter topical 1% cortisol cream. Pirfenidone should be taken with some food to reduce the impact on the stomach and abdominal symptoms. This study was also specifically designed to slowly increase the dose of pirfenidone, monitor for any problems, and adjust the dosing if necessary to help avoid serious problems.

***Rare (infrequent) but serious risks*** experienced by patients taking pirfenidone to treat idiopathic pulmonary fibrosis include:

- Angioedema (swelling of the face, lips, tongue and throat) has rarely been reported in patients (in the range of 1 in 100 to 1 in 1,000 patients) who recently started pirfenidone, usually occurring in the first 90 days of treatment. This condition has not been observed in any patients involved in clinical trials with pirfenidone but should symptoms occur, they require immediate medical attention as swelling of the tongue and throat can be serious and potentially life-threatening.
- Usually, the changes in liver function tests that occur with pirfenidone do not impair liver function, but rarely altered liver function is also observed (an elevated bilirubin test). In all cases that were observed during prior clinical trials, this has been reversible with holding or stopping the medication and it is important to have regular blood test monitoring and to adjust the dose of study drug if asked by your study team to do so. However, in postmarketing reports, very rare cases of atypical drug-induced liver injury have occurred, including severe liver injury with fatal outcome.

**Known risks and discomforts associated with the study tests and assessments:**

Risks associated with randomization:

You will be assigned to a study group at random (by chance). Your assignment is based on chance (like a coin flip) rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. It might also prove to be less effective or have more side effects than the other study group even though information about such an outcome is not currently known.

Loss of confidentiality:

As this study involves the use of your identifiable, personal information, there is a chance that a loss of confidentiality will occur. The researchers have procedures in place to lessen the possibility of this happening (see “How will my information be kept confidential?” section below).

Risks associated with questionnaires:

Questionnaires require that you provide information about your health, how you feel, and how different situations impact on your activity and well-being. Sometimes questions of this type can cause a person to feel anxious or vulnerable. You have the right to refuse to answer any question you do not wish to answer.

Blood draw risks:

Drawing blood may cause temporary pain from the needle stick, bruising or swelling at the site, and rarely, infection or fainting.

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.

HRCT scan risks:

HRCT scans involve exposure to radiation, a form of energy that is known for its potential to cause tissue injury. You are exposed to radiation on a daily basis, both from natural (sun and earth) and manmade sources. The estimated radiation dose that you will receive as a participant for this type of research is compared below to the limits allowed for a radiation worker. This limit for radiation workers is low and is set at a level that is not expected to be harmful. The estimated radiation dose that you will receive as a result of each additional CT scan in this study has been calculated to be about 2.4% of the annual limit allowed radiation workers. One HRCT scan is proposed during the screening phase of the study and a second will occur at completion of the study, 18 months later. The person obtaining your consent can answer any questions you have, and provide more detailed information about the amount of radiation resulting from this study.

Having an HRCT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia or anxiety when placed inside the CT scanner, or by lying in one position for a long time. However, the HRCT protocol included in this study is relatively brief and the time inside the enclosed portion of the scanner is usually no more than a few minutes.

**Unknown risks and discomforts:**

The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

**ARE THERE ANY BENEFITS IF I PARTICIPATE?**

**Possible benefits to me:**

You may not receive any specific benefits from participation in this study. However, if mycophenolate or pirfenidone 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 organ involvement (that is, other organs that have been affected by your scleroderma such as the skin or heart).

**Possible benefits to others or society:**

This study will also help the researchers learn more about these drug treatments. Hopefully this information will help in the treatment of future patients with conditions like yours.

**WHAT OTHER CHOICES DO I HAVE IF I DON'T WANT TO PARTICIPATE?**

If you decide not to take part in this study, or if you withdraw from this study before it is completed, you can still discuss potential alternative treatments with your personal physicians. There is one medication approved by the FDA (nintedanib, brand name Ofev®) that may slow the rate of decline in some aspects of lung function in patients with scleroderma-related interstitial lung disease. Your physicians may be able to prescribe this medication or a course of treatment based on what they decide is in the best interest of your care even if it is not FDA approved. Alternatively, there may be other research studies that offer other forms of experimental therapy that you could consider. Before you decide to take part in this study, you may discuss the benefits and risks of potential alternatives with the study doctor.

**CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?**

The researchers may end your participation in this study for a number of reasons, such as if your safety and welfare are at risk, if you do not follow instructions or if you miss scheduled visits. The researchers or the study sponsor might also decide to stop the study at any time.

If you are asked to permanently discontinue both study drugs for any reason, the researcher will ask you to partake in a close-out telephone interview and return unused study medication. The data collected about you up to the point of withdrawal will remain part of the study and may not be removed from the study database. In addition, you will be asked to return to the clinic for the Month 12 and Month 18 visits that are described above (see section on, "What will happen if I take part in this study"). These additional visits and the data obtained from them will help achieve our research goals even if you are no longer taking study drug. While we ask that you return for these visits if at all possible, you have the right to refuse to complete either one or both of the requested visits.

**HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?**

The researchers will do their best to make sure that your private information is kept confidential. Information about you will be handled as confidentially as possible, but participating in research may involve a loss of privacy and the potential for a breach in confidentiality. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security.

**Storage and use of personal information that can identify you:**

When you receive hospital services, testing and medical evaluations that are intended for your personal medical care, such information will be stored and handled as would any other confidential medical records for hospital and physician services. Information and blood samples that are stored for the purposes of the research study will be coded with a unique study identification number to protect your identity. Personal identify information, such as name and date of birth, will not be attached to such samples or information. However, the UCLA Principal Investigator and the Data Coordinating Center for the study, which is separately located at the University of Michigan School of Public Health, will maintain a link between the code and your personal identifying information. This code will be maintained in a secured and password-protected manner so that only the Principal Director and the Data Coordinating Center Director will have access. Other researchers who may use your samples or information obtained about you during the study will not be provided with the link or any personal identifying information.

**People and agencies that will have access to your information:**

The research team, authorized UCLA personnel, the Data Coordinating Center, and regulatory agencies such as the Food and Drug Administration (FDA), may have access to study data and records to monitor the study. Genentech, Inc., the manufacturer of pirfenidone (Esbriet®), may also have access to study data and records in the event of a required audit or in the course of preparing filings to regulatory agencies such as the FDA. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

**How long information from the study will be kept:**

Research data, records and specimens will be maintained for a period of at least 7 years after the initiation of this research study and may be retained for longer periods if required to achieve the study goals or by regulatory agencies such as the FDA.

**ARE THERE ANY COSTS FOR TAKING PART IN THIS STUDY?**

The study will supply and pay for the cost of supplying and administering the study drugs and extra laboratory tests that are carried out specifically for the research which include the HRCT scan of the chest performed during the screening and at the 18-month visit, and the breathing tests that are performed every 3 months during the course of your participation in the study.

However, you and your insurer may be billed for the costs of all other study procedures and for the costs of any standard medical care that you receive during your participation in the study and you will be responsible for any associated co-payments and deductibles. There is a possibility that your medical insurance company may not cover these costs because you are in a research study. If this happens you might have unexpected expenses from being in this study, such as the costs associated with treating side effects. Financial counseling and itemized cost estimates are available upon request.

**WILL I BE PAID FOR MY PARTICIPATION?**

You will not be paid for your participation in this research study.

**WHAT OTHER THINGS SHOULD I CONSIDER BEFORE PARTICIPATION?**

**Use of My Specimens:**

Any specimens (e.g., tissue, blood, urine) obtained for the purposes of this study will become the property of the University of California. Once you provide the specimens you will not have access to them. The University may share your specimens in the future with other researchers or outside institutions. Information that identifies you will not be shared with anyone outside of UCLA. The specimens will be used for research and such use may result in inventions or discoveries that could become the basis for new products or diagnostic or therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed by the University. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the specimens.

**Researcher Financial Interests in this Study:**

[To be updated by UCLA site investigators as part of their separate IRB application]

**WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?**

**The Research Team:**

You may contact [name(s) to be updated by UCLA site investigators as part of their separate IRB application] at [phone number(s) to be updated by UCLA site investigators as part of their separate IRB application] with any questions or concerns about the research or your participation in this study. You can also call the UCLA Page Operator at (310) 825-6301 to reach [insert name(s)] 24 hours a day, 7 days week.

**UCLA Office of the Human Research Protection Program (OHRPP):**

If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, you may contact the UCLA OHRPP by phone: (310) 825-5344; by email: mirb@research.ucla.edu or U.S. mail: UCLA OHRPP, 11000 Kinross Ave., Suite 211, Box 951694, Los Angeles, CA 90095-1694.

**Public Information about this Study:**

ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

**WHAT HAPPENS IF I BELIEVE I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?**

It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him/her at the number(s) listed above.

If you are injured as a result of being in this study, UCLA will provide necessary medical treatment. The costs of the treatment may be covered by the University of California or billed to you or your insurer just like other medical costs, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For more information about this, you may call the UCLA Office of the Human Research Protection Program at 310-825-5344 or send an email to *mirb@research.ucla.edu*.

**WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?**

Taking part in this study is your choice. You can choose whether or not you want to participate. Whatever decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

- You have a right to have all of your questions answered before deciding whether to take part.
- Your decision will not affect the medical care you receive from UCLA.
- If you decide to take part, you can leave the study at anytime.
- If you decide to stop being in this study you should notify the research team right away. The researchers may ask you to complete some procedures in order to protect your safety.
- If you decide not to take part, you can still get medical care from UCLA.

**HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?**

If you agree to participate in this study you should sign and date below. You have been given a copy of this consent form and the Research Participant's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

**SIGNATURE OF THE PARTICIPANT**

_____
Name of Participant

_____ _____
Signature of Participant Date

Please initial one of the spaces below to indicate whether we may contact you annually for up to 5 years after the study:

___ I agree to be contacted annually for up to 5 years after the study.

___ I decline to be contacted annually for up to 5 years after the study

**SIGNATURE OF PERSON OBTAINING CONSENT**

| _____ | _____ |
|---|---|
| Name of Person Obtaining Consent | Contact Number |
| _____ | _____ |
| Signature of Person Obtaining Consent | Date |

**SCHEDULE OF STUDY VISITS AND ASSESSMENTS**

***SCREENING AND INITIAL 6 MONTHS***

| **Type of Visit:** | **Screen** | **Baseline** | **Phone** | **Regular** | **Phone** | **Regular** | **Regular** | **Regular** | **Regular** | **Regular** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #:** | **S1-2** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| **Study Month:** | | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 5 | 6 |
| | | | | | | | | | | |
| **Assessments** | | | | | | | | | | |
| Medical history | X | X | X | X | X | X | X | X | X | X |
| Physical exam | X | X | | X | | X | X | X | X | X |
| Review Medication | X | X | X | X | X | X | X | X | X | X |
| Describe Adverse events | | | X | X | X | X | X | X | X | X |
| Lung function testing | X | X | | | | | X | | | X |
| Blood sample | X | | | X | | X | X | X | X | X |
| Questionnaires | X | X | | | | | X | | | X |
| HRCT scan of chest | X | | | | | | | | | |
| Pregnancy test* | X | X | | X | | X | X | X | X | X |
| Blood for storage | | X | | | | | | | | |

* For women who are able to become pregnant; require a blood test at screening then urine testing.

***MONTHS 7-19 AND (OPTIONAL) EXTRA FOLLOW-UP FOR 5 YEARS***

| **Type of Visit:** | **Phone** | **Regular** | **Phone** | **One Year** | **Phone** | **Regular** | **Phone** | **18 Month** | **Final Phone** | **Extra** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #:** | **10-11** | **12** | **13-14** | **15** | **16-17** | **18** | **19-20** | **21** | **22** | |
| **Study Month:** | 7, 8 | 9 | 10, 11 | 12 | 13, 14 | 15 | 16, 17 | 18 | 19 | Yrs 2-5 |
| | | | | | | | | | | |
| **Assessments** | | | | | | | | | | |
| Medical history | X | X | X | X | X | X | X | X | X | X |
| Physical exam | | X | | X | | X | | X | | |
| Medication review | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X |
| Lung function testing | | X | | X | | X | | X | | |
| Blood sample | | X | | X | | X | | X | | |
| Questionnaires | | X | | X | | X | | X | | |
| HRCT scan of chest | | | | | | | | X | | |
| Pregnancy test* | | X | | X | | X | | X | | |
| Blood for storage | | | | X | | | | X | | |

* For women who are able to become pregnant; require a blood test at screening then urine testing.

### 13.5 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Michigan Data Coordinating Center. This will not include direct links to the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Michigan Data Coordinating Center research staff will be secured and password protected. At the end of the study when all subject follow-up and analysis is complete, verified and secured, all study databases will be de-identified and archived.

### 13.6 FUTURE USE OF STORED DATA AND SPECIMENS

Data and biological samples collected for this study will be prepared, analyzed and/or stored at the University of Michigan Data Coordinating Center and the UCLA Administrative and Contracting Core, respectively, under the direction of their Directors. After specific phases of the study are completed, as appropriate, the de-identified, archived data and specimens will be available for use by other researchers including those outside of the study. Permission to use data and specimens for such purposes will be provided by consenting participants and included in the informed consent, with such use approved by the appropriate institutional IRBs.

Such data and samples are intended for research into the causes of Scleroderma-associated ILD and its associated conditions, the natural history and biology of the disease, its progression and its treatment.

## 14 DATA HANDLING AND RECORD KEEPING

### 14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Comprehensive data coordinating center (DCC) functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the DSMB will be provided by the University of Michigan Statistical Analysis of Biomedical and Education Research (SABER) group. Housed in the top nationally ranked Department

of Biostatistics, SABER, in its 17-year existence, has served as the DCC for over 50 studies, including multiple NIH-sponsored networks.

The DCC will use OpenClinica® (OpenClinica Clinical Trial Software; OpenClinica, LLC, Waltham, MA), a clinical trial software platform for electronic remote (i.e., site-based entry) data capture and clinical data management, as the basis for our custom-designed data entry and management system. The majority of data will be collected via electronic Case Report Forms (CRFs); however, other data sources, such as laboratory data from the central laboratory, may be used. In these circumstances, the DCC will also utilize electronic data transfer. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the OpenClinica database or data mart.

The DCC has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. OpenClinica® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Operations will provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

## 14.2 STUDY RECORDS RETENTION

Study documents are to be retained for a minimum of 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product for the studied purpose. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or scheduled protocol-required activity. The DCC will also assess compliance with the protocol during its monitoring visits. The DCC will summarize protocol deviations in site performance reports. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

## 14.4 PUBLICATION AND DATA SHARING POLICY

The Faculty of the University of California are committed to disseminating its research and scholarship as widely as possible. In particular, as part of a public university system, the Faculty is dedicated to making its scholarship available to the people of California and the world. Each Faculty member grants

to the University of California a nonexclusive, irrevocable, worldwide license to exercise any and all rights under copyright relating to each of his or her scholarly articles, in any medium, and to authorize others to do the same, for the purpose of making their articles widely and freely available in an open access repository. This policy does not transfer copyright ownership, which remains with Faculty authors under existing University of California policy.

The study will comply with Section 801 of the Food and Drug Administration Amendments Act of 2007, and this clinical trial will be registered in ClinicalTrials.gov, a freely available public registry sponsored by the National Library of Medicine.

In addition, an explicit goal of this study is to present the primary and related outcomes of this study at Scientific Meetings and to publish, as possible, in peer-reviewed Scholarly Journals to assure dissemination of the findings. The authority to do so resides with the participant investigators and not with any sponsor.

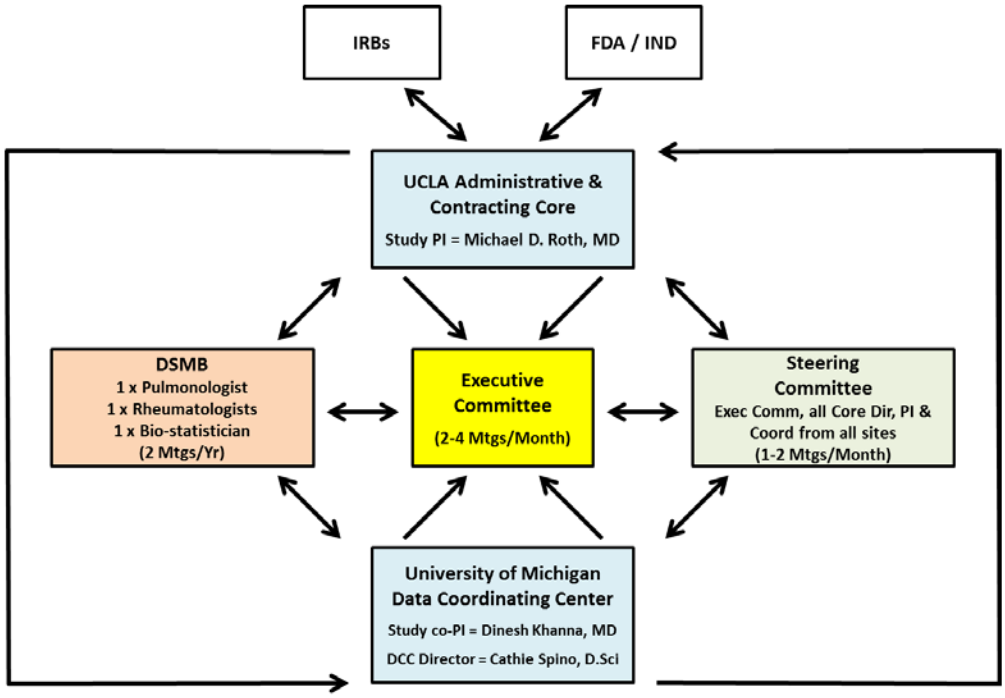
A bio-specimen repository will be created in which de-identified blood speciments and linked clinical and research data will be made available to qualified researchers who submit meritorious applications for the access and use of such samples. Oversight for the review of requests and the dissemination of study materials will be through the Study Executive and Steering Committees and/or any sub-committees that they may appoint for this process.

# 15 STUDY ADMINISTRATION AND OVERSIGHT

## 15.1 STUDY LEADERSHIP

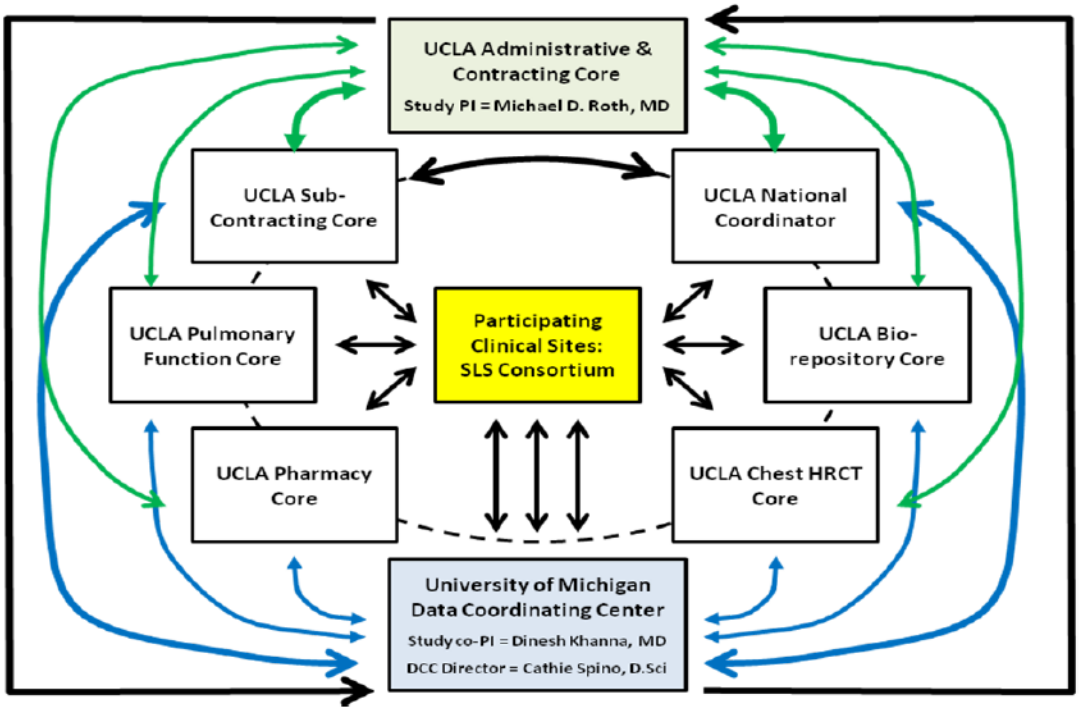
The overall management and day-to-day operational structure proposed for the SLS-III study is outlined in the two organizational charts below (**Figures 15.1A-B**).

**Figure 15.1A: Organizational Chart depicting Study Administrative Oversight and Management**



Note that the Executive Committee (indicated in Yellow) will serve as the central body responsible for oversight and management and will meet every 1 to 2 weeks throughout the 5-year course of the study. It is directly supported in this function by the presence of two Coordinating Units, The UCLA Administrative and Contracting Core and the University of Michigan Data Coordinating Center (highlighted in blue). These three units [Executive Committee; Administrative Core and Data Coordinating Center] are responsible for interacting with the full Steering Committee, which includes representation from every participating clinical site, and with the independent Data, Safety and Monitoring Committee. The UCLA Administrative Core will hold the study IND and the overall study IRB approval and represent the study in those respects.

**Figure 15.1B: Day-to-Day Operational Flow Chart**




Note that in the day-to-day operational flow, the Participating Clinical Sites (indicated in Yellow) serve as the central body responsible for the interaction with study patients and the day-to-day clinical oversight of both patient care and testing. The Clinical Sites are directly supported in their task by the Data Coordinating Center (highlighted in blue), which is responsible for the data collection and monitoring. The UCLA Administrative Core (highlighted in green) only has an indirect role in the day-to-day operations in that it is in constant contact with the Data Coordinating Center and oversees the 6 UCLA Core Services (appear in white) which directly support the day-to-day operations of the Clinical Sites. Should the Data Coordinating Centers or Cores identify day-to-day issues that require input, they are empowered to immediately interact with the UCLA Administrative Core or to address those issues in the regularly scheduled Executive Committee meetings.

### 15.1.1 UCLA Administrative & Contracting Core

The designated Principal Investigator for SLS III will direct the UCLA Administrative and Contracting Core, which will be operationally responsible for all aspects of the clinical trial and contracting with participating clinical sites. The Principal Investigator will be assisted by a National Study Coordinator

with experience in the conduct of scleroderma-associated clinical research and operational familiarity with all administrative and clinical aspects of the clinical trial and the participating sites, investigators and coordinators at participating sites. The Administrative and Contracting Core will be responsible for finalizing the SLS III protocol, IND and ClinicalTrial.gov filings, and overseeing the contracting and reimbursements for all of the sub-contracted clinical sites. In addition to the Contracting Core, the UCLA Administrative and Contracting Core will also oversee essential Core services in support of the study including the provision of a National Study Coordinator and the HRCT QIA Imaging Core, Pulmonary Function QA Core, Pharmacy Core, and a Bio-repository Core, all of which will develop operational guidelines and oversee the services defined by their titles.

### 15.1.2 Data Coordinating Center (DCC)

The Director of the DCC, housed at the University of Michigan within the Statistical Analysis of Biomedical & Educational Research (SABER) Unit of the School of Public Health, will also serve as thes Senior Statistician. The DCC staff will include a Database programmer, Data manager, Statistical Analyst, Project Manager, Clinical Monitor, Web Programmer/Designer, and a Research Administrator. In addition, the Co-PI for the overall studywill be located at the University of Michigan and will act as the on-site Clinical Advisor for the DCC in addition to other responsibilities. 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 Executive Committee, Steering Committee, and DSMB. The Clinical Monitor will interact regularly with the National Study Coordinator at UCLA and in the initial year, will visit all of the clinical sites for on-site monitoring. Subsequent routine monitoring will be done remotely, using regularly scheduled web-based meetings for document and protocol review. The DCC will also evaluate sites for meeting performance goals, completing documentation, and producing reimbursement documents for the Administrative Core at UCLA. The DCC will prepare all of the routine study reports for the Executive Committee, Steering Committee, DSMB, and in support of annual filings with for the IND, etc. The DCC will interact with all of the Cores and send out study notices, including those related to lab alerts, adverse events and SAEs using automated notification networking.

### 15.1.3 Executive Committee

The Executive Committee, chaired by the Principal Investigator for the study, will meet every one-to-two weeks and interact closely with the DCC and the Cores 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 the clinical trial. Other members of the Executive Committee include an Executive Consultant, Study co-PI, and the Director of the DCC, the National Coordinator and ad hoc representation from the Directors of the named Cores as needed. Each Executive Committee meeting will include a review of enrollment, randomization, retention, drop-outs, AEs, SAEs, medication control issues, site performance and problems, Core reports, study compliance issues, and any interval protocol issues.

### 15.1.4 Steering Committee

A Steering Committee chaired by the study Principal Investigator will provide overall scientific direction for the trial with input from the key personnel at each participating study site. Voting members will include the Chairman, one Pulmonary and one Rheumatology investigator from each Clinical Center, the DCC Director, and the Director of each Core. 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 teleconference/web calls for the duration of the trial. The Steering Committee will also have the authority to organize and empower working subcommittees (as needed for the study) including:

- Recruitment and Patient Issues Committee
- Quality Control Committee
- Drug Distribution and Safety Monitoring Committee
- Ancillary Studies Committee
- Manuscript Preparation Committee

### 15.1.5 Data & Safety Monitoring Board (DSMB)

A 3-member external Data and Safety Monitoring Board (DSMB) will be appointed and composed of individuals who have no direct conflicting involvement with the study or an active salaried appointment with any of the participating institutions. The recommended composition of the DSMB will be to include a pulmonologist, a rheumatologist, and a biostatistician with an expectation that each member will have experience in one or more of the following areas:

- interstitial lung disease
- idiopathic pulmonary fibrosis
- systemic sclerosis
- collagen-vascular disease associated ILD
- clinical trial design and management
- data management and statistical analysis
- patient safety monitoring
- the ethical conduct of clinical research
- clinical use of Pirfenidone and/or Mycophenolate

The DSMB Chair will be appointed by the Study Executive Committee from among experts in the field and then recommend the remainder of the Committee Members for consideration by the study Executive Committee using the defined expertise and affiliation criteria.

The DSMB will review the protocol and suggest any changes that might be required prior to its implementation. Once the trial is initiated, the DSMB will review cumulative trial results to evaluate the treatment for beneficial and adverse effects, including the review of all Serious Adverse Events. The board will also monitor the performance of individual clinics and study performance indicators (drug monitoring and compliance, visit compliance, recruitment, etc.). The DSMB will meet every 6 months by teleconference and/or web videoconferencing for the duration of the trial and will interact directly with the Data Coordinating Center for access to study data and interim reports.

The DSMB will be charged to provide external oversight concerning the safety and scientific integrity of the study for the duration of the clinical trial and produce written reports that will advise the sponsor and Executive Committee as to whether the DSMB recommends that the study continue as is, consider specific safety and/or data management changes, or consider early termination due to specific safety or ethical management concerns.

### 15.1.6 Study Cores

The Study Cores are provided as a centralized resource that will a) develop and disseminate operational guidelines for their areas of expertise; b) provide site training in their areas of expertise; c) deliver key services, d) and provide standardization and quality assurance. The Core Directors will be members of the Executive Committee in order to completely integrate these aspects of study services and oversight into the overall flow and oversight of the Clinical Trial. The Study Cores are:

- **Contracting Core:** Uniform contracting guidelines and assurances will be developed and executed with each of the participating clinical sites to carry out the described clinical trial. With data input from the Data Coordinating Center, the Contracting Core will also approve site expenditures and reimbursements for the performance of study services.
- **National Study Coordinator:** The National Study Coordinator acts as a core resource to liason between the Investigators and Administration of the study and the actual performance of the clinical trial by the site personnel. The National Study Coordinator will help to standardize and distribute regulatory documents, including IRB consents and drug safety notifications, and lead regular meetings of the study coordinators from all participating sites so that lessons and experiences at each site can be shared with the other sites, which is key in the study of an orphan disease where patient numbers and individual experience are limiting features. The National Study Coordinator also acts as a readily available resource to field and trouble-shoot day-to-day operational issues that arise in the conduct of the study.
- **HRCT QIA Imaging Core:** The Imaging Core will include a Director, research physicist, coordinators and staff that are responsible for establishing and overseeing the CT imaging protocol including the development of the manual of operations, interacting with radiologists and technicians at each site to categorize, standardize and program their equipment for participation in the imaging protocol, and will assure that HIPAA compliant protocols are in place for data transfer and storage. In addition to these aspects of raw data acquisition, the imaging core will be responsible for carrying out the quantitative image analysis required for all CT data sets and for assessing and reporting quality assurance and compliance with operational guidelines. If imaging problems should arise, they will work with an individual site to identify and resolve these issues.
- **Pulmonary Function QA Core:** In addition to preparing a PFT manual of operations and helping to establish satisfactory standardization and quality of PFT tests performed at all clinical centers, the PFT Core will review all patient test results for completeness, compliance with protocol requirements, and accuracy. If deficiencies should arise, the Core Director will work one-on-one with a site to establish the reason and resolution of such deficiencies. If repeat testing is required, the PFT Core Director will communicate this information to the Data Coordinating Center and to the site.
- **Pharmacy Core:** The Investigational Drug Unit of the Department of Pharmaceutical Services, University of California Los Angeles, at the Ronald Reagan Medical Center will

serve as the central drug packaging and distribution site for all participating institutions. Responsibilities include drug procurement, storage and inventory, drug accountability and drug distribution to all participating sites. They will establish the operational procedures by which all sites will receive, label and distribute drug supply for the study, but each site will be responsible for drug inventory control, distribution and disposal at their individual sites after receipt of study drug from the Core.

- **Bio-repository Core:** The UCLA Bio-repository Core will establish standard procedures and train sites for the collection, processing, storage and shipping of blood samples from study patients. They will provide centralized kits and instructions and also house the returned sample in a secure storage system at UCLA for later use. They will track performance and provide inventory control and also, when applicable, at the direction of the Executive Committee, distribute samples to individual investigators for analysis.

## 15.2 PROCEDURE FOR PROTOCOL MODIFICATION

Modifications 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 Study Executive Committee 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 initially be submitted to the DSMB for review and until their recommendations for further modification have been addressed or it is approved. Once DSMB approval has been obtained, the revised Protocol and the List of Changes will be submitted to the FDA and to the IRBs at all participating clinical sites. 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 if indicated by the nature of the requested change and the instructions of the FDA and/or responsible IRB.

# 16 CONFLICT OF INTEREST POLICY

## 16.1 COMPLIANCE WITH 21 CFR PART 54

The investigators and sponsors will comply with the FDA regulations governing financial disclosure by clinical investigators, 21 CFR part 54, in case a new drug application should be filed in conjunction with the work supported by this clinical trial. As per the regulations, applicants will certify the absence of certain financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA, or alternatively disclose those financial interests and arrangements to the agency and identify steps taken to minimize the potential for bias (21 CFR § 54.4(a)).

### 16.1.1 Disclosable Financial Interests & Arrangements under 21 CFR part 54

The financial interests, arrangements, and payments that must be disclosed (see 21 CFR § 54.4(a)(3), referred to herein as “disclosable financial interests and arrangements”) are described below.

16.1.1.1 Any compensation made to the investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.

16.1.1.2 A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.

16.1.1.3 Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

16.1.1.4 Any equity interest in any sponsor of the covered study if the sponsor is a publicly held company and the interest exceeds $50,000 in value. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

16.1.1.5 Significant payments of other sorts (SPOOS) are payments that have a cumulative monetary value of $25,000 or more and are made by any sponsor of a covered study to the investigator or the investigator's institution during the time the clinical investigator is carrying out the study and for one year following completion of the study. This would include payments that support activities of the investigator (e.g., a grant to the investigator or to the institution to fund the investigator's ongoing research or compensation in the form of equipment), exclusive of the costs of conducting the clinical study or other clinical studies, or to provide other reimbursements such as retainers for ongoing consultation or honoraria. See Section IV, Questions C.4, C.5, and C.6 for additional information on SPOOS.

### 16.1.2 Completion of Forms FDA 3455 & 3454 under 21 CFR part 54

For each clinical investigator [a "listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects," including the spouse and each dependent child of the investigator or subinvestigator] who is not identified as an employee of the sponsor, one of the following must be submitted (21 CFR § 54.4(a)):

16.1.2.1 FORM FDA 3455 Disclosure Statement. Form 3455 shall be completed for each clinical investigator who, or whose spouse or dependent child, had disclosable financial interests in and/or arrangements with any sponsor of the covered clinical study. The form should include an attachment with detailed information about those financial interests and arrangements and a description of the steps taken to minimize the potential for bias resulting from the disclosed financial interests and arrangements (21 CFR § 54.4(a)(3)).

16.1.2.2 FORM FDA 3454 Certification Form 3454 shall be completed for any clinical investigator who has no disclosable financial interests in or arrangements with any sponsor of the covered clinical study (21 CFR § 54.4(a)(1)); the applicant may append a list of investigator names to a single FORM FDA 3454 for those investigators with no disclosable financial interests or arrangements.

### 16.2 COMPLIANCE WITH LOCAL STATE AND UNIVERSITY REGULATIONS & POLICY

In addition to FDA regulations, Investigators at the University of California Los Angeles will follow UCLA Procedure 925.2: Disclosing Financial Interests in Non-Governmental Sponsors of Contracts, Grants, and Material Transfer Agreements for Research. In addition, Investigators at the Data Coordinating Center and all participating clinical sites will be held to their applicable local State and University Conflict of Interest Regulations and Policies. Compliance will be certified as a condition of sub-contract awards.

## 17 EMERGENCY DISASTER/PANDEMIC MANAGEMENT PLAN

Emergency disasters, including infectious outbreaks such as the Coronavirus Disease 2019 (COVID-19) pandemic, may disrupt patient access or the capacity for institutions to provide usual study care. Modifications to normal study operations including inclusion and exclusion criteria, screening and randomization, handling of study drugs, study visits, testing and site monitoring may be required in order to protect patients and maintain the integrity of the clinical trial.

The emergency procedures described herein may be activated by the Executive Committee and implemented as needed, in whole or in part and for an appropriate duration, in order to respond to the specific circumstances imposed by the emergency.

The declaration of an emergency situation and details regarding the exact components of the protocol that will be modified in response to the situation, will be codified in the Manual of Operations and distributed as Emergency Updates to all participating clinical sites, study investigators and staff, and study cores.

Provisions that may be required to immediately protect patient well-being, as determined by study investigators, may be immediately implemented. However, activation of an Emergency Disaster/Pandemic Management Plan and the exact details of that plan are to be reported in a timely manner to the local IRB, the SLS III DSMB and to the FDA if required by the nature of the changes.

Once activated, the specific provisions of the Emergency Disaster/Pandemic Management Plan will supercede normal study operations until the emergency is declared over by the Executive Committee. While the Emergency Disaster/Pandemic Management Plan is active, following the provisions of that management plan will be considered consistent with the official Study Protocol and not designated as protocol deviations. The Data Coordinating Center will track related compliance and any missing study data due to the emergency.

### 17.1 MODIFICATIONS TO INCLUSION AND EXCLUSION CRITERIA

During an emergency, protocol-defined inclusion and exclusion criteria (detailed in the Protocol Sections 5.1 and 5.2) will be reviewed to determine whether modifications are required. Such determinations will be based on the nature of the emergency and a resulting need to assure the safety of study participants and/or the integrity of the study.

Potential modifications may include the following examples (not intended to be an exclusive list):

a) The age of study participants if required to protect the safety of an identified population at risk during the emergency.
b) Testing for exposure to, or the presence of, an infection as may be required in a pandemic situation.

c) Additional screening blood tests or modification of existing allowable test thresholds (for example, allowable liver function or blood counts) as may be required to reduce or eliminate a disaster-specific risk.

## 17.2 DETERMINATION OF RISK AND OPTIONS FOR MANAGEMENT OF STUDY DRUGS

In an emergency situation, the Executive Committee will review the safety profile for the study drugs and discuss the impact of any emergency guidelines issued by the FDA, Center for Disease Control (CDC) or related health advisory organization and determine whether the indications or contraindications for study drugs have changed and whether the nature of the emergency will impact on patient participation in the study. Patient safety during an emergency will be considered the first priority. All active study participants will be notified of potential risk to them posed by the emergency and the options for management of study drugs and/or their continued participation in the study. If necessary, study drugs may be shipped to patients during an emergency when on-site visits are not possible or not advised due to the nature of the emergency.

### 17.2.1 Risk assignment during COVID-19 pandemic

a) According to the CDC, adults age 65 or older, those with underlying lung disease, heart disease or diabetes, and individuals with an identified immune deficit are considered "at high risk" for complications from COVID-19 infection.
b) Due to the presence of underlying lung disease in all study participants and their treatment with a study drug with immunosupressive properties, all active study participants will be notified that their underlying condition and its treatment according to the study define them as being "at high risk" for infectious complications from COVID-19 according to CDC criteria.

### 17.2.2 Options for management of study drugs during COVID-19 pandemic

a) Participants will be encouraged to follow all Center for Disease Control (CDC) and local public health guidelines to reduce exposure risk.
c) In the absence of evidence that withdrawing treatment for their lung disease is advisable, participants who are asymptomatic (from infectious perspective) are not recommended to stop study medication.
d) However, subjects will be advised to communicate any fever or cold symptoms such as cough, chills or new shortness of breath with the local study team and their treating physicians as soon as possible.
e) Section 6.1.5.2 of the SLSIII protocol will be followed for dose management recommendations in the event of any signs of active infection. Per protocol and local investigator discretion, MMF may be held during an infection and doing so in this case should be considered in a timely manner.
f) Study participants will be advised, as already noted in their signed study consent, that participation in the study is voluntary and participants may decide to withdraw from drug treatment or the entire study at any time.
g) While we are not advising the prophylactic suspension of MMF at this time, study participants are allowed to be off MMF for up to 60 days related to potential tolerability or toxicity issues and remain in the study (Section 6.1.5.1.i ). Any study participant that holds or suspends study drugs in this setting will be notified of their options and invited to remain in the study regardless of their decision about continuing with study drugs (see Protocol Section 7.2.5).

### 17.2.3 Dispensing of study drugs during COVID-19 pandemic

Due to the impact of COVID-19 on the operation of participating clinical sites and the perceived risk for study participants in attending Medical Center visits during the pandemic, study drugs will be shipped as needed to the participant's home after completion of required "remote visit".

a) Remote visits are required (as detailed in Section 17.4 below) to assess drug compliance and assure the safety of continued drug administration before prescribing.
b) Shipping of study drugs will require inventory control measures and verification that study drugs were received by the participant.

## 17.3 IMPACT OF THE EMERGENCY ON SCREENING AND RANDOMIZATION

During an emergency, the ability to screen or randomize patients may be impaired due a disruption of services offered at a participating clinical site, issues with patient access, or concerns regarding the safety associatd with initiation of therapy during the emergency. Options to be considered include:

a) Proceed with screening and/or randomization if, after notification and consultation with the patient, it is determined to be in the patient's best interest to do so and if the participating clinical site can safely proceed and complete all of the study requirements.
   - A remote visit (as detailed in Section 17.4 below) may be utilized for aspects of the screening and randomization visits, but completion of the informed consent, screening vitals and physical examination must be completed in person.
   - Completion of required pulmonary function testing, mRSS test, and thoracic HRCT must be completed in person in order to meet eligibility criteria.
b) Delay the completion of scheduled screening visits or planned randomizations to a later time if the patient will be able to complete randomization within the allowed 90 days from the initiation of screening visit #1.
c) Cancel further screening or randomization visits until such time as resources are available or it is deemed safe to proceed. Any participant who has their screening or randomization cancelled should be considered for re-screening when the emergency ends, but would be required to meet study inclusion and exclusion criteria at that time.

## 17.4 ALLOWABLE MODIFICATIONS TO STUDY VISITS AND PROCEDURES

Study operations may be placed on complete hold or suspended during an emergency when institutional closures and/or perceived risk to the study population prohibit the safe conduct of the study. This determination will be made by the Executive Committee and carried out in conjunction with review by institutional IRBs and the SLS III DSMB, who will be provided with a study closure mitigation plan to address participant notification and referral to alternative care providers if possible under the circumstances. An early termination visit will be carried out as per Protocol Section 7.2.4 when possible.

Alternatively, the study may convert in person (on-site) study visits to "remote study visits" in order to compensate for emergency issues that limit either institutional or patient access.

### 17.4.1 Conversion from in person to remote study visits

a) Screening, baseline and follow-up visits, regardless of whether in person or remote, are to be carried out within established visit windows.

b) When an in person visit is converted to a remote visit, this may be carried out using a formal telemed or video conference system or by simple phone contact between the study staff and the study patient.
   - Regardless of the mechanism employed, the remote visit encounter must be accompanied by appropriate source documentation.
   - Study records should indicate when an in person visit is converted to a remote visit.
   - Study records should indicate whenever specific components of a study visit cannot be completed remotely due to the activation of the emergency protocol.

c) Pre-specified phone follow-up visits are to continue as indicated in Section 7.2.3.3.

### 17.4.2 Components of study visits that can be carried out remotely

a) Patient history or interim history.
   - Proceed using telemed, video or phone visits

b) Review of concomitant medications
   - Proceed using telemed, video or phone visits

c) Assessment of adverse events
   - Proceed using telemed, video or phone visits

d) Modified study drug reconciliation
   - Proceed using telemed, video or phone visits
   - Review patient drug diary in detail and have patient provide copy for record if possible
   - Have participant describe available medication supply
   - Direct pill counts will not be possible

e) Toxicity monitoring and pregnancy testing utilizing available commercial laboratories
   - Arrange for particpant to have complete blood count with differential and platelet count, comprehensive metabolic panel and pregnancy testing completed at any available clinical laboratory
   - Pregnancy test may be carried out by qualitative urine or blood test as available
   - All clinical lab results must be collected and retained as source documents

f) Study drug dispensing
   - Once a remote visit has been carried out and toxicity monitoring reviewed and approved, study drug may be shipped to the participant as detailed in Section 17.2.3

g) Patient reported outcomes (PROs)
   - Email or mail (with return envelope and postage) visit-specific questionnaires to participants to complete and follow-up with them within 7 days to assure that participants have completed and returned them.
   - If preferred by participant or coordinator, questionnaires may be administered over the phone with the coordinator asking questions verbatim and stating all potential choices before recording participant responses.
   - Note that the SHAQ VAS page cannot be completed by phone; either mail the DCC provided form to the participant or skip its administration.

h) Modified Mahler Transitional Dyspnea Index
   - Complete the Mahler TDI, if required for the visit, by phone

i) Physician and Patient Global Assessments
   - Proceed using telemed, video or phone visits

### 17.4.3 Components of study visits that cannot be carried out remotely

Components of study visits that require direct examination or on-site completion may not be available during an emergency due to limitations in institutional or patient access. These components cannot be carried out remotely (by telephone or video visits) and the inability to complete will require deviation from that described in Protocol Section 7.2, Study Schedule. Absence of the following test results for a remote visit should be so noted in the study record as due to "COVID-19 Restrictions" or other emergency situation to address this deviation. Missing assessments may be collect out of window or at next on-site study visit, if appropriate.

a) Physical examination
b) mRSS
c) Pulmonary function tests (spirometry and DLCO).
d) Thoracic HRCT
e) Blood collection for Biological Specimen Repository

### 17.4.4 Completion of pulmonary function tests at a remote facility

Pulmonary function tests are an established standard of care test for patients with SSc-ILD and required at routine intervals to monitor patients for the state of their lung disease, inter-current illnesses and treatment failures that might warrant additional evaluation and/or management.

In the setting of prolonged restrictions on travel or institutional access, or when ongoing safety concerns limit the ability for participating study patients to complete these outcome assessments at their assigned clinical site, the Executive Committee may allow such testing to be completed at a remote facility. Testing at remote facilities should be carried out in accord with ATS standards and by Certified Pulmonary Function Technologists. All requests for remote PFTs must be reviewed and approved in advance by the Executive Committee. Testing will be carried out as a recommended standard-of-care clinical assessment and therefore completed at the discretion of the study participant after being informed of the indications and potential financial implications. Data generated from such assessments may be included as official study outcome measures if reviewed by the Pulmonary Function QA Core and determined to meet minimum quality and reproducibility requirements.

## 17.5 REVISED SITE MONITORING

On-site monitoring visits may not be possible during an emergency. The Data Coordinating Center will utilizing remote monitoring with remote source data verification, as required, to maintain oversight of clinical sites as outlined in Protocol Section 9, CLINICAL MONITORING.

Given the potential impact of an emergency situation on institutional resources, study personnel and the capacity to schedule and travel to visits, the time windows for the completion of study visits (as detailed in Protocol Section 7) may be extended by up to 30 days at the discretion of the Executive Committee. Decisions regarding the length of extended visit windows will take into account issues such as availability/access for visits, patient safety monitoring, standard-of-care and the presence of adequate study drug reserves.

# 18 LITERATURE REFERENCES

1. Atanelishvili I, Liang J, Akter T, Spyropoulos DD, Silver RM, Bogatkevich GS. Thrombin increases lung fibroblast survival while promoting alveolar epithelial cell apoptosis via the endoplasmic reticulum stress marker, CCAAT enhancer-binding homologous protein. Am J Respir Cell Mol Biol. 2014;50(5):893-902.
2. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, Sato A, Kudoh S. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005 May 1;171(9):1040-7.
3. Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Current Opinions in Rheum 2012:24(2):165-170.
4. Baroni SS, Santillo M, Bevilacqua F, Luchetti M, Spadoni T, Mancini M, Fraticelli P, Sambo P, Funaro A, Kazlauskas A, Avvedimento EV, Gabrielli A. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med. 2006;354(25):2667-76.
5. Beretta L, Santaniello A, Lemos A, et al. Validity of the Saint George's Respiratory Questionnaire in the evaluation of the health-related quality of life in patients with interstitial lung disease secondary to systemic sclerosis. Rheumatology 2007; 46(2):296-301
6. Bouros D, Wells AU, Nicholson AG, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002; 165:1581-1586.
7. Clements PJ, Roth MD, Elashoff R, Tashkin DP, et al. for the Scleroderma Lung Study. Differences in the presentation and course of patients with limited versus diffuse Systemic sclerosis. Ann Rheumatic Dis 2007; 66(12):1641-7
8. Colic M, Stojic-Vukanic Z, Pavlovic B, et al. Mycophenolate mofetil inhibits differentiation, maturation and allostimulatory function of human monocyte derived dendritic cells. Clin Exper Immunol 2003; 134:63-69.
9. D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. Am J Med. 1969 Mar;46(3):428-40.
10. Denton CP. Scleroderma Lung Study II—clarity or obfuscation? Lancet Respir Med. Published online ahead of press: 25 July 2016, http://dx.doi.org/10.1016/S2213-2600(16)30191-6.
11. Esbriet (pirfenidone) Investigator's Brochure (RO0220912), Eleventh Version, F. Hoffmann-La Roche Ltd, July 2016.
12. Esbriet Package Insert, NDA-022535, Genentech Inc., Approved Oct 15, 2014
13. Fan MH, Feghali-Bostwick CA, Silver RM. Update on scleroderma-associated interstitial lung disease. Curr Opin Rheumatol. 2014;26(6):630-6.
14. Furst DE, Tseng CH, Clements PJ, Strange C, Tashkin DP, Roth MD, Khanna D, Li N, Elashoff R, Schraufnagel DE; Scleroderma Lung Study. Adverse events during the Scleroderma Lung Study. Am J Med. 2011; 124(5):459-67.
15. Gardner RM, Clausen JL, Epler GR, Hankinson JL, Permutt S, Plummer AL. Pulmonary function laboratory personnel qualifications. Am Rev Respir Dis 1986; 134:623-4.
16. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj A, Bozovic G, Denton CP, Black CM, du Bois RM, Wells AU. Interstitial lung disease in

systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 2008 Jun 1;177(11):1248-54. doi: 10.1164/rccm.200706-877OC. Epub 2008 Mar 27.

17. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med 1999; 159:179-187.

17a. Hankinson JL, Kawut SM, Shahar E, et al. Performance of American Thoracic Society-Recommended Spirometry Reference Values in a Multiethnic Sample of Adults : The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. Chest 2010; 137:138-145.

18. Hinchcliff ME, Beaumont JL, Carns MA, Podlusky S, Thavarajah K, Varga J, Cella D, Chang RW. Longitudinal evaluation of PROMIS-29 and FACIT-dyspnea short forms in systemic sclerosis. J Rheumatol. 2015 Jan;42(1):64-72. doi: 10.3899/jrheum.140143. Epub 2014 Nov 1.

19. Hoyles RK, Ellis RW, Wellsbury J, et al. Fibrosing Alveolitis in Scleroderma Trial (FAST) – a multi-centre, prospective, randomized, double-blind, placebo-controlled trial of treatment with corticosteroids and intravenous cyclophosphamide followed by oral azathioprine. Arth Rheum 2006; 54:3962-70.

20. Khanna D, Albera C, Fischer A, N. Khalidi, G. Raghu, L. Chung, D. Chen, E. Schiopu, 8, E. Gorina, M. Tagliaferri, J. R. Seibold. Safety And Tolerability Of Pirfenidone In Patients With Systemic Sclerosis-Associated Interstitial Lung Disease - The Lotuss Study. Am J Respir Crit Care Med 191;2015:A1175

21. Khanna D, Berrocal VJ, Giannini EH, Seibold JR, Merkel PA, Mayes MD, Baron M, Clements PJ, Steen V, Assassi S, Schiopu E, Phillips K, Simms RW, Allanore Y, Denton CP, Distler O, Johnson SR, Matucci-Cerinic M, Pope JE, Proudman SM, Siegel J, Wong WK, Wells AU, Furst DE. The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. Arthritis Rheumatol. 2016 Feb;68(2):299-311. doi: 10.1002/art.39501.

22. Khanna D, Furst DE, Hays RD, et al. Minimally important difference in diffuse systemic sclerosis: results of the D-penicillamine study. Ann Rheum Dis 2006;65:1325-9.

23. Khanna D, Furst DE, Maranian P, Seibold JR, Impens A, Mayes MD, Clements PJ, Getzug T, Hays RD. Minimally important differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. J Rheumatol. 2011 Sep;38(9):1920-4. doi: 10.3899/jrheum.110225. Epub 2011 Jul 1.

24. Khanna D, Hays RD, Maranian P, Seibold JR, Impens A, Mayes MD, Clements PJ, Getzug T, Fathi N, Bechtel A, Furst DE. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Arthritis Rheum. 2009 Sep 15;61(9):1257-63. doi: 10.1002/art.24730.

25. Khanna D, Tseng CH, Furst DE, et al. Minimally important differences in the Mahler's Transition Dyspnoea Index in a large randomized controlled trial—results from the Scleroderma Lung Study. Rheumatology (Oxford) 2009;48:1537-40.

26. Khanna D, Yan X, Tashkin DP, Furst DE, Elashoff R, Roth MD, Silver R, Strange C, Bolster M, Seibold JR, Riley DJ, Hsu VM, Varga J, Schraufnagel DE, Theodore A, Simms R, Wise R, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, Rothfield N, Metersky M, Clements PJ; Scleroderma Lung Study Group. Impact of oral cyclophosphamide on health-related quality of life in patients with active scleroderma lung disease: results from the scleroderma lung study. Arthritis Rheum. 2007; 56:1676-84.

27. Kim HJ, Brown MS, Elashoff R, Li G, Gjertson DW, Lynch DA, Strollo DC, Kleerup E, Chong D, Shah SK, Ahmad S, Abtin F, Tashkin DP, Goldin JG. Quantitative texture-based assessment of one-year

changes in fibrotic reticular patterns on HRCT in scleroderma lung disease treated with oral cyclophosphamide. Eur Radiol. 2011 Dec;21(12):2455-65. doi: 10.1007/s00330-011-2223-2. Epub 2011 Sep 17.

28. Kim HJ, Tashkin DP, Gjertson DW, Brown MS, Kleerup E, Chong S, Belperio JA, Roth MD, Abtin F, Elashoff R, Tseng CH, Khanna D, Goldin JG. Transitions to different patterns of interstitial lung disease in scleroderma with and without treatment. Ann Rheum Dis. 2016 Jul;75(7):1367-71. doi: 10.1136/annrheumdis-2015-208929. Epub 2016 Jan 12.
29. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014 May 29;370(22):2083-92.
30. Leconte S, Ferrant D, Dory V, Degryse J. Validated methods of cough assessment: a systematic review of the literature. Respiration. 2011;81(2):161-74. doi: 10.1159/000321231. Epub 2010 Nov 13. Review.
31. Little RJA. (1993). Pattern-mixture models for multivariate incomplete data. Journal of the American Statistical Association 88:125-134.
32. Ludwicka A, Ohba T, Trojanowska M, Yamakage A, Strange C, Smith EA, Leroy EC, Sutherland S, Silver RM. Elevated levels of platelet derived growth factor and transforming growth factor-beta 1 in bronchoalveolar lavage fluid from patients with scleroderma. J Rheumatol. 1995 Oct;22(10):1876-83.
33. MacIntyre N, Crapo RO, Viegi G, et al. Standarisation of the single-breath determination of carbon monoxide uptake in the lung. (ATS/ERS Task Force: Standardisation of Lung Function Testing). Eur Respir J 2005; 26:720-735.
34. Miller MR, Hankinson J, Brusasco V, et al. Standadisation of spirometry. (ATS/ERS Task Force: Standardisation of Lung Function Testing). Eur Respir J 2005; 26:319-338.
35. Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V, Byron J, Sahhar J, Roddy J, Gabbay E, Youssef P, Nash P, Zochling J, Proudman SM, Stevens W, Nikpour M. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology (Oxford). 2013;52(1):155-60.
36. Nagai S, Hamada K. Shigematsu M, et al. 2002. Open-label compassionate use one-year treatment with pirfenidone to patients with chronic pulmonary fibrosis. Intern Med 41: 1118-1123.
37. Neas LM, Schwartz J. The determinants of pulmonary diffusing capacity in a national sample of US adults. Am J Respir Crit Care Med 1996; 153:656-64.
38. Nikpour M, Baron M. Mortality in systemic sclerosis: lessons learned from population-based and observational cohort studies. Curr Opin Rheumatol 2014; 26(2):131-7.
39. Noble PW, Albera C Bradford WZ. et al. 2011. Pirfenidone in patients with idiopathic pulmonary fibrosis CAPACITY): Two randomised trials. Lancet 377: 1760-1769.
40. Pattanaik D, Brown M, Postlethwaite BC, Postlethwaite AE. Pathogenesis of Systemic Sclerosis. Front Immunol 2015; 6:272.
41. Pellegrino R, Viegi G, Brusasco V, Crapo RO, et al. Interpretative strategies for lung function tests. (ATS/ERS Task Force: Standardisation of Lung Function Testing). Eur Respir J 2005; 26:948-68.

42. Petty TL. The National Mucolytic Study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest. 1990;97(1):75-83

43. Raghu G1, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study.Am J Respir Crit Care Med. 1999 Apr;159(4 Pt 1):1061-9.

44. Roth MD, Tseng CH, Clements PJ, Furst DE, Tashkin DP, Goldin JG, Khanna D, Kleerup EC, Li N, Elashoff D, Elashoff RM; Scleroderma Lung Study Research Group. Predicting treatment outcomes and responder subsets in scleroderma-related interstitial lung disease. Arthritis Rheum. 2011; 63(9):2797-808.

45. Rubin D. (1976). Inference and missing data (with discussion). Biometrika 63:581-592.

46. Steen VD, Conte C, Owens GR, Medsger TA Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994; 37: 1283-1289.

47. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum. 2000 Nov;43(11):2437-44.

48. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1997–2002. Ann Rheum Dis 2007; 66:940–944.

49. Taniguchi H, Ebina M, Kondoh Y, et al. 2010. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 35:821-829.

50. Tashkin DP, Elashoff R, Clements PJ, et al. for the Scleroderma Lung Study (SLS) Research Group. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007 177(10): 1026.

51. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, Arriola E, Silver R, Strange C, Bolster M, Seibold JR, Riley DJ, Hsu VM, Varga J, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, Rothfield N, Metersky M for the Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006; 354:2655-66.

52. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, MD, Kleerup EC, Goldin J, Arriola E, Volkmann ER, Kafaja S, Silver R, Steen V, Strange C, Wise R, Wigley F, Mayes M, Riley DJ, Hussain S, Assassi S, Hsu VM, Patel B, Phillips K, Martinez F, Golden J, Connolly MK, Varga, MD J, Dematte J, Hinchcliff ME, Fischer A, Swigris J, Meehan R, Theodore A, Simms R, Volkov S, Schraufnagel DE, Scholand MB, Frech T, Molitor JA, Highland K, Read CA, Fritzler MJ, Kim GHJ, Tseng C-H, Elashoff RM, for the Sclerodema Lung Study II Investigators. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016 Sep;4(9):708-19.

53. Theodore AC, Tseng CH, Li N, Elashoff RM, Tashkin DP. Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: findings from the Scleroderma Lung Study. Chest. 2012 Sep;142(3):614-21.

54. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, Bancel DF, Allanore Y, Müller-Ladner U, Distler O, Iannone F, Pellerito R, Pileckyte M, Miniati I, Ananieva L, Gurman AB, Damjanov N, Mueller A, Valentini G, Riemekasten G, Tikly M, Hummers L, Henriques MJ, Caramaschi P, Scheja A, Rozman B, Ton E, Kumánovics G, Coleiro B, Feierl E, Szucs G, Von Mühlen CA, Riccieri V, Novak S, Chizzolini C, Kotulska A, Denton C, Coelho PC, Kötter I, Simsek I, de la Pena Lefebvre PG, Hachulla E, Seibold JR,

Rednic S, Stork J, Morovic-Vergles J, Walker UA. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010; 69(10):1809-15.

55. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA Jr, Carreira PE, Riemekasten G, Clements PJ, Denton CP, Distler O, Allanore Y, Furst DE, Gabrielli A, Mayes MD, van Laar JM, Seibold JR, Czirjak L, Steen VD, Inanc M, Kowal-Bielecka O, Müller-Ladner U, Valentini G, Veale DJ, Vonk MC, Walker UA, Chung L, Collier DH, Ellen Csuka M, Fessler BJ, Guiducci S, Herrick A, Hsu VM, Jimenez S, Kahaleh B, Merkel PA, Sierakowski S, Silver RM, Simms RW, Varga J, Pope JE. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013 Nov;72(11):1747-55.
56. Varga J. Systemic sclerosis: an update. Bull NYU Hosp Jt Dis. 2008;66(3):198-202.
57. White B. Pulmonary fibrosis and pulmonary vascular involvement in systemic sclerosis. 9a. Pulmonary fibrosis in systemic sclerosis. In Systemic Sclerosis, 2nd edition (PJ Clements, DE Furst, edit). Lippincott, Williams, & Wilkins, New York, NY. 2004:163-183.
58. Winstone TA, Assayag D, Wilcox PG, Dunne JV, Hague CJ, Leipsic J, Collard HR, Ryerson CJ. Predictors of mortality and progression in scleroderma-associated interstitial lung disease: a systematic review. Chest. 2014;146(2):422-36.

## APPENDIX LIST

| Version | Date | Description | Significant Revisions |
|---|---|---|---|
| 1.0 | 04/25/17 | App #A: Study Questionnaires | |
| 1.1 | 07/2019 | App #B: Drug Packaging Inserts | Pirfenidone (Esbriet) drug packaging insert updated |