Title: A phase two randomized, double-blinded, placebo-controlled study combining physiological, radiographic, and biological biomarkers to study the anti-fibrotic effect of pirfenidone in CLAD post lung-transplantation

PI: Vibha N. Lama, M.D., M.S.

ID: HUM00131610

NCT: NCT03473340

IRB Approval Date: 5/11/2019

CLINICAL TRIAL PROTOCOL

Title:	A phase two randomized, double-blinded, placebo-controlled study combining physiological, radiographic, and biological biomarkers to study the anti-fibrotic effect of pirfenidone in CLAD post lung-transplantation	
Brief Title:	Role of pirfenidone in treatment of lung transplant rejection	
Clinical Phase:	II	
Coordinating Investigator	Vibha N. Lama, M.D., M.S. Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine University of Michigan Health System 1150 W. Medical Center Drive 6301 MSRB III Ann Arbor, MI, 48109-0644	
Status:	Final	
Version and Date:	Version: 2.0	Date: January 31, 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company	Genentech
Name of finished product:	pirfenidone
Name of active ingredient	pirfenidone
Protocol date:	January 31, 2019
Title of Trial:	A phase two randomized, double-blinded, placebo-controlled study combining physiological, radiographic, and biological biomarkers to study the anti-fibrotic effect of pirfenidone in CLAD post lung-transplantation
Coordinating investigator:	Vibha N. Lama, M.D., M.S.
Trial site:	University of Michigan
Clinical phase:	Phase II
Objective:	To evaluate the efficacy and safety of pirfenidone 801 mg TID over 24 weeks in lung transplant recipients with chronic lung allograft dysfunction
Methodology:	Single centre, placebo-controlled, randomized, double-blinded, clinical trial comparing safety and efficacy of Pirfenidone 801 mg TID to placebo over 24 weeks in patients with chronic lung allograft dysfunction (CLAD)
Number of patients	60 (30 per group)
Treatments:	pirfenidone: 2403 mg daily placebo: 2403 mg daily
Diagnosis:	Spirometric and clinical diagnosis of CLAD
Main inclusion criteria:	- Patients > 6 months after lung transplantation with documented baseline values of FEV_1 and FVC (mean of two highest value measured 3 weeks apart) - Baseline FEV_1 and FVC > 50% predicted (to assure viable graft) - Diagnosis of CLAD (two consecutive spirometric values with FEV_1 alone or both FEV_1 and FVC < 80% of baseline)
Endpoints/Outcomes:	Primary: - Change in functional small airways disease (fSAD) as measured by parametric response mapping (PRM) at 24 weeks by treatment arm Secondary: - Change in FEV_1 over 24 weeks by treatment arm - Change in FVC over 24 weeks by treatment arm - Number of subjects with treatment intolerance - Number of subjects with adverse events related to treatment with Pirfenidone Exploratory: - Change in bronchoalveolar lavage (BAL) mesenchymal colony forming units (CFUs) by treatment arm - Change in fibrotic phenotype of BAL mesenchymal cells (expression of collagen, alpha smooth muscle actin, beta-catenin, fibronectin) by treatment arm
Safety criteria:	- Vital signs, physical examination - Clinical laboratory tests (hepatic function tests, creatinine) - Reporting of adverse events

<table>
<tr><td></td><td></td></tr>
<tr><td>Statistical Methods:</td><td>We will describe the distribution of fSAD change within and between treatment groups (n=30 per group) over a 6-month period. Preliminary data suggests that without treatment, fSAD increases 9% on average over a 6-month time period with SD of 9%. If pirfenidone halves this increase over 6 months, we would have a confidence interval for the treatment effect of 4.5+/-4.64%. Power to detect 6-month treatment differences is sensitive to assumptions of the standard deviation above and the ability of pirfenidone to reduce 6-month fSAD progression; a power analysis table is given below for various effect sizes and standard deviations that might be seen in the trial based on a sample size of 60 (30 per group).
<table>
<tr><td></td><td colspan="3">% Increase in FSAD for Pirfenidone Group (vs 9% FSAD increase in Placebo Group)</td></tr>
<tr><td>Std Dev</td><td>0%</td><td>2%</td><td>4.5%</td></tr>
<tr><td>5</td><td>>99%</td><td>>99%</td><td>93%</td></tr>
<tr><td>7</td><td>>99%</td><td>97%</td><td>69%</td></tr>
<tr><td>9</td><td>97%</td><td>84%</td><td>48%</td></tr>
</table>
We will similarly summarize changes in spirometric parameters and MSC CFU and phenotype over time between and within groups.

We do not anticipate any significant drop out because of the short duration of the study and this specific patient population who receive their clinical care at a specialized lung transplant center with no loss to follow up.</td></tr>
</table>

TABLE OF CONTENTS

DEFINITIONS AND ABBREVIATIONS

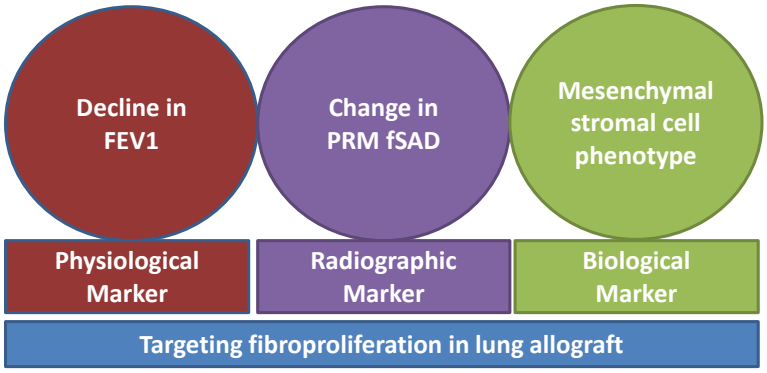
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AR	Acute rejection
ATG	Antithymocyte Globulin
AST	Aspartate aminotransferase
BAL	Bronchoalveolar lavage
BOS	Bronchiolitis obliterans syndrome
CFU	Colony forming units
CLAD	Chronic lung allograft dysfunction
COPD	Chronic obstructive pulmonary disease
DSMB	Data Safety Monitoring Board
ECP	Extracorporeal photopheresis
EKG	Electrocardiogram
EOS	End of study
EOT	End of treatment
FEV1	Forced expiratory volume in 1 second
fSAD	Functional small airways disease
FVC	Forced vital capacity
HRCT	High resolution computed tomography
IMP	Investigational Medicinal Product
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional review board
LFT	Liver function test
MSC	Mesenchymal stromal cells
OTIS	Organ Transplant Information System
NIH	National Institutes of Health
PFT	Pulmonary Function Tests
PI	Principal investigator
PRM	Parametric response mapping
RAS	Restrictive allograft syndrome
ULN	Upper limit of normal
UM	University of Michigan

1. SPECIFIC AIMS

Aim 1. To determine if pirfenidone compared to placebo will stabilize progression of functional small airways disease (fSAD) as measured by parametric response mapping (PRM), a novel CT-based biomarker.

Aim 2. To determine if pirfenidone therapy will stabilize pulmonary function as measured by FEV_1 and FVC in lung transplant recipients with chronic lung allograft dysfunction (CLAD).

Aim 3. To investigate if pirfenidone therapy affects the fibrotic phenotype of mesenchymal cells collected from bronchoalveolar lavage (BAL).



2. BACKGROUND/RATIONALE/PRELIMINARY STUDIES

Our principle hypothesis is that pirfenidone therapy will stabilize lung function decline and slow progression of fSAD in lung transplant recipients with CLAD.

Greater than 50% of lung transplant recipients show signs of CLAD by 5 years post-transplantation (1). This process arises from development of graft fibrosis in a peri-bronchial (bronchiolitis obliterans or BO), peri-vascular, or fulminant interstitial and airway luminal fibrosis distribution (2, 3). Therapies to prevent or slow CLAD are lacking. Anti-fibrotic therapies may offer an avenue to prevent progression of CLAD and prolong allograft survival.

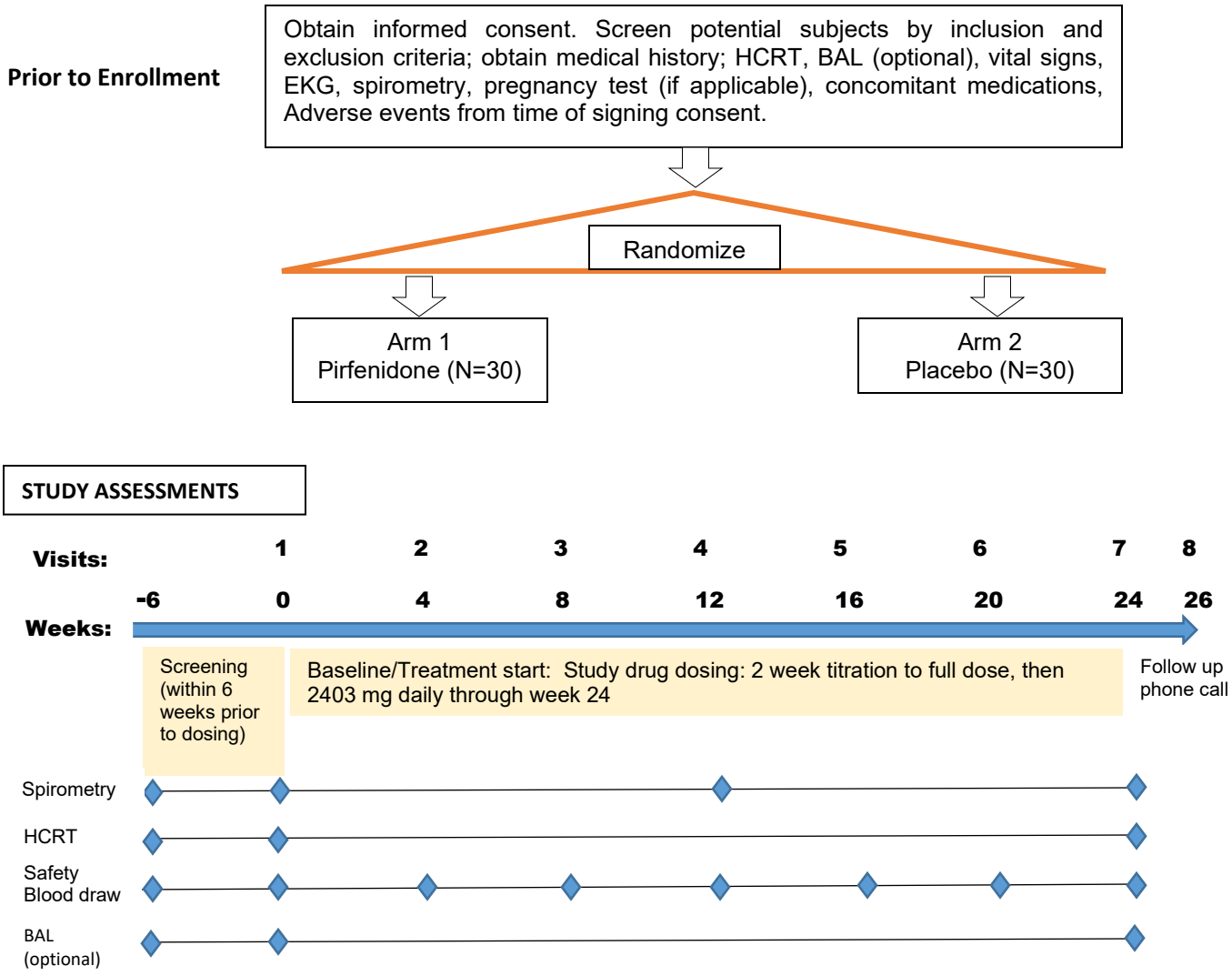
Pirfenidone, an oral anti-fibrotic agent, was approved for treatment of idiopathic pulmonary fibrosis (IPF) in 2014. In large multi-center, international clinical trials, pirfenidone has been shown to reduce the rate of FVC decline in patients with IPF with a favorable safety and tolerability profile (4, 5).

Small airways, the predominant histologic target of fibrotic remodeling in a chronically rejecting lung allograft, have been termed the “silent zone” of the lung secondary to difficulty in evaluating this disease process by pathology or imaging (6). While high resolution CT (HRCT) scans are routinely obtained at CLAD onset, HRCT findings in CLAD lack specific diagnostic features, and small airways cannot be visualized or evaluated by standard methods.

A novel imaging technology to evaluate functional small airways disease (fSAD) has been developed and validated at the University of Michigan. This technology, termed parametric response mapping (PRM), utilizes voxel by voxel comparison of inspiratory and expiratory HRCT images through co-registration to provide quantitative measures of fSAD. This tool has been utilized in patients with a variety of lung diseases including patients with chronic obstructive pulmonary disease (COPD) and lung transplant recipients (7-9). Higher levels of fSAD in lung transplant recipients with CLAD has been associated with decreased survival, and fSAD values have been shown to increase over time compared to transplant patients without chronic rejection (8, 9). We propose to utilize this novel imaging biomarker to track the change in fSAD, as it relates to change in traditional measures of FEV_1 or FVC, in patients with CLAD enrolled in this clinical trial. We have significant experience in longitudinal monitoring of lung function and have been pioneers in describing the natural history of spirometric decline after CLAD onset (10). Imbio Platform systems, a commercial company with quantitative image biomarker algorithms, will be utilized in this study.

Furthermore, this study will employ a novel biological biomarker of fibroproliferation, mesenchymal stromal cells (MSCs), in assessing the effect of pirfenidone on CLAD. Use of this biomarker is based on 10 years of work in our lab demonstrating that MSCs can be isolated from BAL of lung transplant recipients and are biomarkers of BOS (11, 12). The number of MSCs can be quantitated by a colony forming assay and now as a nested PCR based mRNA measure of unique lung-MSC transcription factors Foxf1 (11). The third aim of this study will investigate the effect of pirfenidone on MSC number and phenotype. This will be the first study analyzing novel imaging and MSC biologic markers of fibroproliferation following administration of a therapeutic agent for CLAD.

Schematic of Study Design



3. INVESTIGATORS' EXPERIENCE IN SUBJECT AREA

This study has two Co-Principal Investigators:
Dr. Vibha N. Lama, M.D., M.S. (Co-Principal Investigator) is the Henry Sewell is the Henry Sewall Research Professor of Pulmonary and Critical Care Medicine and Professor of Internal Medicine at University of Michigan. She serves as the Associate Chief of Basic and Translational Research in the Division of Pulmonary & Critical Care Medicine. Dr. Lama is an internationally renowned physician researcher in the field of lung transplantation and has contributed immensely to the field of chronic lung allograft dysfunction or specifically bronchiolitis obliterans syndrome. She is a trained clinical translational physician scientist with a Master's degree in biostatistics and clinical study design at the University of Michigan School of Public Health. Dr. Lama is an R0-1 funded independent researcher and is the associate director of lung transplant research at University of Michigan.

Dr. Kevin Flaherty M.D., M.S. (Co-Principal Investigator) is currently a Professor of Internal Medicine at the University of Michigan. Over the past 15 years he has developed a scholarly niche in the study and care of patients with interstitial lung diseases. He has served in leadership roles for industry and National Institutes of Health (NIH) sponsored trials of novel treatments for IPF. He also directs the University of Michigan Destination program for Interstitial Lung Diseases and serves as Steering Committee Chair of the Pulmonary Fibrosis Foundation Clinical Care Network/Patient Registry. Dr. Flaherty also serves as vice-chair for the University of Michigan Human Subjects Institutional Review Board. The University of Michigan has been a leading recruiter of subjects with IPF and thus has extensive experience in the design and conduct of clinical trials. Dr. Flaherty is an active member of the University of Michigan lung transplant team caring for lung transplant patients for over 15 years. Dr. Flaherty will aid in the development of the final clinical trial protocol and actively recruit and enroll subjects from the University of Michigan into this clinical trial evaluating the potential therapeutic role of pirfenidone for the slowing of progression of CLAD.

The study team will also include University of Michigan Medicine pulmonologists experienced in lung transplant and clinical trials, who will serve as sub-investigators. These physicians have used pirfenidone for other pulmonary diseases. They will aid in recruitment of patients and perform study assessments.

4. EXPERIMENTAL DESIGN

4.1 ENDPOINTS

Primary:

- Change in functional small airways disease (fSAD) as measured by parametric response mapping (PRM) at 24 weeks by treatment arm

Secondary:

- Change in FEV_1 over 24 weeks by treatment arm
- Change in FVC over 24 weeks by treatment arm
- Number of subjects with treatment intolerance over 24 weeks
- Number of subjects with adverse events related to treatment with Pirfenidone

Exploratory:

- Change in bronchoalveolar lavage (BAL) mesenchymal colony forming units (CFUs) by treatment arm
- Change in fibrotic phenotype of BAL mesenchymal cells (expression of collagen, alpha smooth muscle actin, beta-catenin, fibronectin) by treatment arm

4.2 STUDY DESIGN

Single center, randomized, double-blind placebo controlled clinical trial of pirfenidone for the attenuation of progression of fSAD in lung transplant recipients with CLAD. A total of 60 patients will be enrolled in the trial.

Eligible patients will be randomized 1:1 to receive either pirfenidone 801 mg TID or placebo.

4.3 INCLUSION CRITERIA

- Lung transplant recipients 18 years of age or older.
- Greater than 6 months after single or bilateral lung transplantation
- Baseline FEV_1 and FVC values (mean of two highest value measured 3 weeks apart) > 50% predicted (to assure viable graft)
- Diagnosis of CLAD (two consecutive spirometric values of FEV_1 alone or both FEV_1 and FVC < 80% of baseline)

4.4 EXCLUSION CRITERIA

- Acute Rejection (AR) diagnosis by biopsy in the 28 days prior to enrollment
- Treatment with pulse steroids, Anti-thymocyte Globulin (ATG), extracorporeal photopheresis (ECP), plasmapheresis, or Immunoglobulin therapy aimed at CLAD within the 28 days prior to enrollment
- If the subject is receiving chronic Azithromycin therapy, the dose must be stable for the 28 days prior to enrollment
- Presence of active pulmonary infection at the time of enrollment as determined by an investigator in consultation with the treating pulmonologist
- Diagnosis of bronchial stenosis either a) requiring stenting, or b) thought to be responsible for the spirometric decline by principal investigator
- Abnormal liver function tests (AST or ALT > 2 x upper limit of normal (ULN), Alkaline phosphatase > 2.5 x ULN, total bilirubin > ULN) or known cirrhosis (>2 times upper limit of normal of AST/ALT/AP)
- Total WBC < 3.0 K/uL
- Moderate to Severe Renal insufficiency (CrCl <15 mL/min calculated by the Cockcroft-Gault equation)

- Use of any medication known to cause significant interactions with pirfenidone (strong CYP1A2 inhibitors such as Fluvoxamine or Enoxacin or inducers)
- Pregnancy or lactation. Women of child-bearing potential will have a pregnancy test at enrollment and must agree to maintain highly effective contraception with two methods of birth control from the date of consent through the end of the study.
- Tobacco use within 6 months
- History of alcohol abuse in the past 1 year as determined by the treating pulmonologist
- Any condition other than CLAD that will likely result in death in the next 1 year
- Any condition in the judgement of the principal investigator that would preclude participation in this study
- EKG with QTc interval > 500 msec at screening
- Listed for repeat lung transplantation

Excluded therapies:
The following therapies are not permitted during the study:

Investigational therapy, enrollment in another therapeutic clinical trial within 30 days or 5 half-lives of study medication (whichever is longer)

- Fluvoxamine

5.0 STUDY VISITS

5.1 Screening

Lung transplant recipients at the University of Michigan will be screened by the study team for participation in this trial. If deemed eligible, subjects will be approached regarding study, and the consent form as well as inclusion and exclusion criteria will be reviewed.

Screening Visit (Performed up to 6 weeks prior to baseline visit and initial study drug dosing)
The following procedures will be completed at screening:

- Obtain and document informed consent
- Obtain sex, race, ethnicity, date of birth
- Vital signs (height, weight, temperature, blood pressure, heart rate, respiratory rate, pulse oximetry)
- Review medical history, including transplant history
- Review current medications
- Date of spirometric decline (defined as date of first spirometric measurement used to document spirometric decline) and CLAD phenotype
- Review of bronchoscopy results (if performed in the 6 weeks prior to screening visit)
- Blood draw for screening labs
    - AST, ALT, AP, total bilirubin, creatinine

Screening Bronchoscopy
Bronchoscopy is often employed in routine clinical care to evaluate decline in lung function in lung transplant patients. The University of Michigan (UM) has a standing Institutional Review Board (IRB) approved protocol that that allows for use of BAL fluid for research purposes. If clinical bronchoscopy has been performed within 6 weeks of screening, and no clinical indications of new infection are present (as determined by the principal investigator in consult with the treating pulmonologist), we will utilize the MSC results for this study. If bronchoscopy has not been performed, it may be done following screening and before enrollment, as an

optional part of this study. The informed consent document includes opt in/opt out language for bronchoscopy.

5.2 Baseline Assessment (Visit 1, Week 0)

At the time of baseline, the coordinator will document the following:

- Vital signs (weight, temperature, blood pressure, heart rate, respiratory rate, pulse oximetry)
- Physical exam including general appearance, HEENT, cardiovascular, pulmonary, abdominal, neurologic, dermatologic, and musculoskeletal exams
- Current medications
- Safety blood work for renal and liver evaluation
    - AST, ALT, AP, total bilirubin, creatinine
- Review bronchoscopy results (if performed)
- ECG
- Perform spirometry
- Undergo an HRCT scan with inspiratory and expiratory image acquisition (if HRCT was not done in preceding 6 weeks)
- Serum pregnancy test (if applicable)
- Review adverse events

5.3 Visits 2, 3, 5, 6 (Weeks 4, 8, 16, 20): may be performed at study center or by local lab draw in conjunction with phone visit

- Safety labs to monitor renal and liver function - AP, ALT, AST, total bilirubin, creatinine
- Review hospitalizations
- Review medication compliance
- Review concomitant medications
- Review adverse events

5.4 Visit 4 (Week 12):

- Vital Signs (weight, temperature, blood pressure, heart rate, respiratory rate, pulse oximetry)
- Physical exam including general appearance, HEENT, cardiovascular, pulmonary, abdominal, neurologic, dermatologic, and musculoskeletal exams
- Safety blood work for renal and liver evaluation
    - AP, ALT, AST, total bilirubin, creatinine
- Spirometry
- ECG
- Review hospitalizations
- Review medication adherence
- Review concomitant medications
- Review adverse events

5.5 Visit 7 (Week 24):

- Vital Signs (weight, temperature, blood pressure, heart rate, respiratory rate, pulse oximetry)
- Physical exam including general appearance, HEENT, cardiovascular, pulmonary, abdominal, neurologic, dermatologic, and musculoskeletal exams
  Safety blood work for renal and liver evaluation

    - AP, ALT, AST, total bilirubin, creatinine
- Spirometry
- ECG
- HRCT scan
- Review hospitalizations
- Review medication adherence
- Review concomitant medications
- Review adverse events
- Collect unused study medication and return to investigational pharmacy
- Bronchoscopy with consent of patient and primary physician if no contraindication identified

5.6 Visit 8 (Week 28) (Phone visit):

At the 28 week phone visit, the coordinator will:

- Review hospitalizations
- Review adverse events
- Collect vital status

5.7 Early discontinuation

All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject. If study treatment is discontinued, participants will be asked to continue with study assessments as planned including the HRCT at week 24 as per protocol.

5.8 Randomization

This is a randomized, double-blind, placebo-controlled multi-center study. Assignment to study treatment will be blinded to the study subjects, investigational site personnel, study vendors, and the Sponsor study team, except for the delegated personnel who will review and check the randomization and drug allocation for accuracy.

All patients will be randomized at the Baseline visit, using stratified block randomization with undisclosed block sizes. The stratification factor is FEV1 first vs concurrent FEV1 and FVC decline at time of CLAD onset. Our statistician, Dr. Murray, will assist with randomization. She will provide the Research Pharmacy (via email) with randomization codes for two separate strata as mentioned above. Within each stratum the statistician will indicate treatment assignment“Active Pirfenidone” or “Placebo” and treatment label ID number. The Research Pharmacist (RP) will be told upon patient entry the stratum to which the patient belongs, identifying the appropriate randomization list for each patient. The RP will then dispense Active or Placebo based on the randomization code on the randomization list. The RP will refer to the randomization code at each dispensing.

In the event of a medical emergency in which breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the study statistician for that subject.

Table 1. Schedule of Assessments

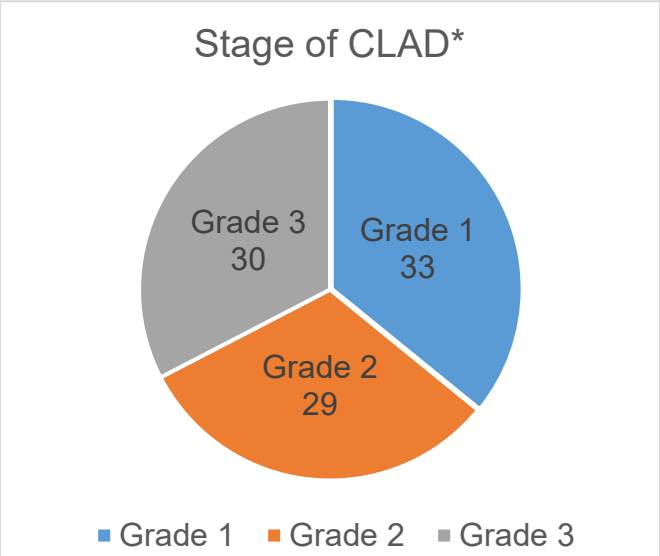
Visit	**Screening[A]**	**1 Baseline**	**2[B] +/- 7days**	**3[B] +/- 7days**	**4 +/- 14days**	**5[B] +/- 7days**	**6[B] +/- 7days**	**7 EOT +/- 14days**	**8 EOS +/- 7days**
Week	**-6 - 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28[C]**
Inclusion/exclusion criteria	x								
Informed consent	x								
Randomization		x							
Demographics	x								
Vital Signs	x	x			x			x	
Physical exam	x	x			x			x	
Medical history	x	x							
Adverse events	x	x	x	x	x	x	x	x	x
Non-elective hospitalizations		x	x	x	x	x	x	x	x
Medication Compliance			x	x	x	x	x	x	
Concomitant medications	x	x	x	x	x	x	x	x	
Pregnancy test[D]		x							
Standard of care labs including immunosuppressive drug levels	x	x	x	x	x	x	x	x	
Safety labs (LFTs)[F]	x	x	x	x	x	x	x	x	
Spirometry	x				x				
Full PFTs		x						x	
HRCT[G]		x						x	
EKG		x			x			x	
Bronchoscopy with BAL[H]	x	x						x	
Vital status assessment									x

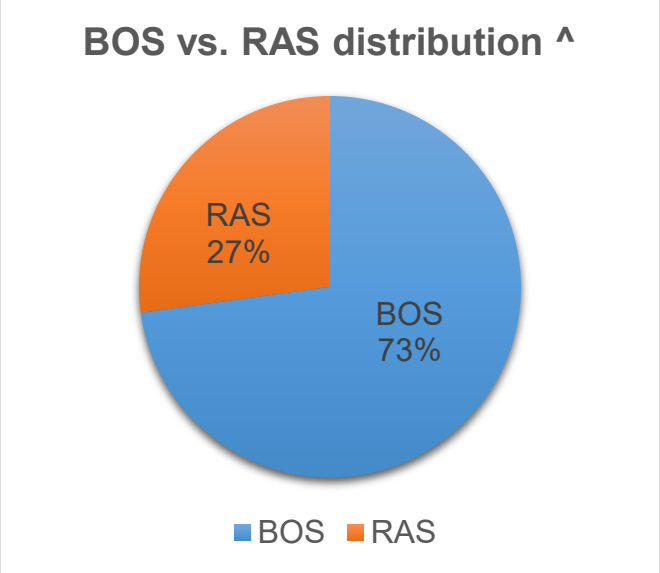
A The time period between the screening and enrollment visit may be up to 6 weeks
B Weeks 4, 8, 16, 20: Laboratory testing may be performed locally
C Week 28 visit may be performed as a telephone visit
D In women of child-bearing potential
E Immunosuppression drug levels will be collected and managed per standard of care
F LFTs will be monitored monthly
G HRCT may be done between screening visit and enrollment (visit 1)
H Results of BAL, if performed per standard of care, will be utilized as baseline if performed within the 6 weeks prior to baseline visit. Other bronchoscopies are optional.

6. RECRUITMENT

University of Michigan has in place a unique prospectively collected dataset of lung transplant patients (Organ Transplantation Information System (OTIS) database). We have, as a part of this database, devised a system in which every patient's baseline lung function post-transplant is analyzed to generate their baseline FEV1 as well as their CLAD status. The trial's study team will screen lung transplant patients using this program to identify potential subjects.

We have run this profile once to determine if recruitment of 60 CLAD patients is viable in the planned two years. At present among all alive patients with lung transplant at our center, 92 patients meet spirometric criterion for CLAD. Phenotype and grade distribution are shown below:





* CLAD grade is based on ISHLT definition. The study plans to include all patients with diagnosis of CLAD irrespective of the stage. Fibroproliferative remodeling in a transplanted lung is an ongoing event as evidenced by continued progressive decline in lung function, worsening of small airway obstruction, and evidence of change in the phenotype of mesenchymal cells isolated from BAL of these patients. It is important that an anti-fibrotic agent be effective at all stages of CLAD because patients can present in any stage of CLAD at the very disease onset. Furthermore, CLAD becomes a chronic disease and patients can survive for prolonged periods of time after onset of CLAD. Hence, the ability of an anti-fibrotic agent to halt fibroproliferation at various time points after onset of CLAD is of key significance.

^ CLAD is identified by decline in FEV1 below 80% of post-transplant baseline as per ISHLT definition. Our published work has shown that patients can present either as an isolated decline in FEV1 (BOS) or as a concurrent decline in both FEV1 and FVC, also termed restrictive allograft syndrome (RAS).[10] As both of these presentations arise from fibrosis, we will not limit our study to one specific phenotype.

7. TIMELINE

Based on the present design and assessment of our center's patient population with CLAD, we estimate the study duration will be 2 years. Patient enrollment can start as soon as regulatory agency approval is obtained (IRB). We have experienced clinical coordinators in our transplant center. Mary Maliarik Ph.D., the clinical coordinator for the trial, has conducted lung transplant studies with Dr. Lama for nearly a decade. Dr. Flaherty and Dr. Belloli are both transplant pulmonologists and are committed to this trial. Dr. Susan Murray Sc.D. is an experienced biostatistician whose area of expertise is clinical trials and she has worked extensively with lung transplant cohorts. In summary, all infrastructure is already in place allowing for rapid start of the proposed clinical trial.

8. DRUG DOSAGE & ADMINISTRATION

Dosage and Administration

	Pirfenidone	Placebo
Substance	Pirfenidone	-
Pharmaceutical formulation	Capsule	Capsule
Source	Genentech	Genentech
Unit strength	267 mg	267 mg
Route	Oral	Oral
Dosage		
Days 1 through 7	267 mg three times daily	267 mg three times daily
Days 8 through14	534 mg three times daily	534 mg three times daily
Days 15 onward	801 mg three times daily	801 mg three times daily

- Take with food.
- Upon initiation of treatment, titrate to the full dosage of 2403 mg/day over a 14-day period as above.

8.1 Adverse reactions

The most common adverse reactions (≥10%) are liver problems, photosensitivity, rash, abdominal pain, nausea, vomiting, diarrhea, dyspepsia, fatigue, headache, dizziness, anorexia, sinusitis, insomnia, weight loss, and arthralgia. These possible adverse events are documented in the informed consent.

Management of abnormal liver function tests

Elevated ALT, AST, and bilirubin elevations have occurred with pirfenidone and will be monitored monthly as above. The investigator will monitor patients for toxicities.

The following protocol will be followed for management of elevation in AST, ALT, and total bilirubin:

Magnitude of AST or ALT elevation	**Recommendation**
3 to 5 x ULN	Confounding medications should be discontinued if clinically indicated, other causes excluded, and the patient monitored closely. The dose of study treatment may be reduced or interrupted if clinically appropriate, with subsequent repeat titration to full dose, as tolerated
≤5 x ULN accompanied by symptoms or hyperbilirubinemia (>2x ULN)	Study treatment should be permanently discontinued
>5 x ULN	Study treatment should be permanently discontinued

Management of photosensitivity and rash

Photosensitivity and rash have been noted with pirfenidone. Patients will be instructed to avoid exposure to sunlight and sunlamps. Patients will be instructed to wear sunscreen (sun

protection factor 50 or higher) and protective clothing daily. Temporary dosage reductions or discontinuations may be required.

If a patient experiences significant rash or photosensitivity, treatment of symptoms and/or temporary dose reductions, interruptions, or discontinuation of study treatment should be considered.

Management of gastrointestinal disorders
Nausea, vomiting, diarrhea, dyspepsia, gastroesophageal reflux disease, and abdominal pain have occurred with pirfenidone. Temporary dosage reductions or discontinuations may be required.

Dosage Modification due to Drug Interactions
Ciprofloxacin is a moderate CYP1A2 inhibitor. With the use of ciprofloxacin at a dosage of 750 mg twice daily, reduce pirfenidone to 534 mg three times a day (1602 mg/day).

EKG abnormalities
If the QTc interval is > 550 msec, this should be confirmed with a repeat EKG within 24 hours. The study drug should be interrupted until the repeat EKG reading. If QTc is still >550 msec than cardiology will be consulted and drug discontinued if abnormality persists.

If the QTc interval is between 500 and 550 msc, confirmed by a repeat EKG within 24 hours, and verified by a local cardiologist, study treatment should be interrupted. If an alternative explanation is identified (electrolyte abnormality or concomitant medication), the study treatment may be re-initiated at the investigator's discretion in consultation with the medical monitor.

9. DRUG STORAGE & HANDLING

Pirfenidone capsules and film-coated tablets are packaged in high-density polythylene bottles with a child-resistant closure system.

Hard capsules should be stored under the recommended storage conditions “Do not store above 30 degrees C”. Film-coated tablets should be stored under the recommended storage condition “Do not store above 25 degrees C”.

For batch specific instructions on storage and information on shelf-life, see the packaging.

The Michigan Medicine Research Pharmacy is responsible for developing and implementing procedures for the proper control and handling of investigational drugs, including procurement, storage, medication labeling and dispensing, drug inventory management, and other distribution and control functions. Information on a drug accountability log includes but is not limited to: receipt date, dispensation date, patient identifier, quantity, lot number, expiration date, and dispenser's initials. Appropriate inventory levels will be maintained by RP to ensure availability of study drugs. As indicated by the sponsor, outdated study medications will be returned by RP to the study sponsor or destroyed.

Drug shipping information:
University of Michigan Hospitals
Department of Pharmacy Services-Research Pharmacy
UHB2D400
1500 East Medical Center Drive
Ann Arbor, MI 48109-5008

Phone: (734) 936-7469

10. DATA ANALYSIS

10.1 Overview

Our Endpoints are:
Primary:
- Change in functional small airways disease (fSAD) as measured by parametric response mapping (PRM) at 24 weeks by treatment arm

Secondary:
- Change in FEV_1 over 24 weeks by treatment arm
- Change in FVC over 24 weeks by treatment arm
- Number of subjects permanently discontinuing study medication before 24 weeks
- Number of subjects with one or more serious adverse events

Exploratory:
- Change in bronchoalveolar lavage (BAL) mesenchymal colony forming units (CFUs) by treatment arm
- Change in fibrotic phenotype of BAL mesenchymal cells (expression of collagen, alpha smooth muscle actin, beta-catenin, fibronectin) by treatment arm

10.2 Sample Size Justification

We will describe the distribution of fSAD change within and between treatment groups (n=30 per group) over a 6-month period. Preliminary data suggests that without treatment, fSAD increases 9% on average over a 6-month time period with SD of 9%. If pirfenidone halves this increase over 6 months, we would have a confidence interval for the treatment effect of 4.5+/-4.64%. Power to detect 6-month treatment differences is sensitive to assumptions of the standard deviation above and the ability of pirfenidone to reduce 6-month fSAD progression; a power analysis table is given below for various effect sizes and standard deviations that might be seen in the trial based on a sample size of 60 (30 per group).

	% Increase in FSAD for Pirfenidone Group (vs 9% FSAD increase in Placebo Group)		
Std Dev	0%	2%	4.5%
5	>99%	>99%	93%
7	>99%	97%	69%
9	97%	84%	48%

We will similarly summarize changes in spirometric parameters and MSC CFU and phenotype over time between and within groups.

While the above power is shown with 60 patients (30 per group), we will plan to enroll 66 patients (33 per group) to account for subject drop out.

10.3 Primary Endpoint Analysis

We believe the data obtained from our study will provide important radiographic and biological signals regarding the efficacy of pirfenidone. We expect a lower SD as the patient population selected will be much better phenotyped for CLAD presence. The high SD in the preliminary data came from patients who improved over time as this data is derived from patients who had CT scans available as routine care rather than in our study where they will be done prospectively. Furthermore, if fibrotic remodeling by pirfenidone is effective we can potentially even see a decrease in fSAD.

We believe that this CT based novel methodology to evaluate small airway disease will provide us with much stronger signal over 6-month period than FEV1 which reaches a floor effect. So the disease progresses even though FEV1 changes are not very evident ultimately leading to graft failure and death. Furthermore, our ability to isolate mesenchymal cells from BAL offers a first unique scenario to directly study the anti-fibrotic effect of pirfenidone.

This trial will also provide information regarding the tolerance of pirfenidone in a lung transplant population who already take multiple medications with serious possible side effects. Tolerance of pirfenidone in addition to baseline transplant medications will be assessed.

Secondary:

- Change in FEV_1 over 24 weeks by treatment arm (e.g, percent or time weighte)
- Change in FVC over 24 weeks by treatment arm
- Number of subjects with treatment intolerance over 24 weeks
    - *Measured by elevated AST, ALT, total bilirubin that results in dose reduction or discontinuing study treatment (the 3 – 5 or greater ULN)*
- Number of subjects with Adverse events related to treatment with Pirfenidone
    - Safety of pirfenidone will be measured by adverse events determined to be related to the study drug as determined by the principal investigator through

review of medical history, physical exam and laboratory findings *or be measured by liver and renal function tests, physical exam*

-

11. SAFETY REPORTING OF ADVERSE EVENTS

11.1 Assessment of safety

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLAD that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

11.2 Methods And Timing For Assessing And Recording Safety Variables

The 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 Genentech, Inc. in accordance with CFR 312.32

11.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of any study procedures and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

11.2.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the {study drug} (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the {study drug}, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the {study drug}; and/or the AE abates or resolves upon discontinuation of the {study drug} or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

11.3 Procedures For Eliciting, Recording, And Reporting Adverse Events

11.3.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

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

11.3.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. 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, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 30 days after the last dose of study drug, a report should be completed and expeditiously submitted 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.

Additional information on any pirfenidone exposed pregnancy and infant will be requested by GenentechDrug Safety at specific time points (i.e. after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior {study drug} exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

h. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product

For this study, there are no AESIs.

I. Adverse Event Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

650-238-6067

Serious adverse events (SAEs), pregnancy reports and AEs of special interest (AESIs), where the patient has been exposed to the Product, will be sent on a MedWatch or CIOMS I form to the Genentech contact specified in Addendum 2 of this SDEA. Transmission of these reports

(initial and follow-up) will be either electronically or by fax and within the timelines specified below:]

- **SADRs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Pregnancy reports**
  While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Special situation reports
In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
- Lack of therapeutic efficacy

In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

j. Aggregate Reports

Dr Lama will forward a copy of the Final Study Report to Genentech upon completion of the Study.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics

- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm115894.htm

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of pirfenidone. An unexpected adverse event is one that is not already described in the pirfenidone Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

FDA fax: **1-800-FDA-0178.**

Genentech Drug Safety Fax: 650-238-6067
Phone: 1-888-835-2555

15 Calendar Day Written Report

RANDOMIZATION CODES FOR BLINDED CLINICAL TRIALS (IF APPLICABLE)

The blind will be broken only in the case of emergent situations in which the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding will be documented in source documents.

Drug Safety:

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

Fax: **650-238-6067**

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

11.4 Data Safety Officer

The Safety Officer will be responsible for assessing subject safety, and monitoring overall conduct and integrity of the study. In fulfilling these responsibilities, the safety officer may make recommendations concerning: recruitment, retention and management of participants; data quality; study compliance; and continuation or stopping of the study.

The Safety Officer will specifically review adverse event data as well as summary reports of all serious adverse events (SAEs) and available lab data, and may review the medical records of individual cases if deemed appropriate or necessary to determine if a safety concern is emerging. The Principal Investigators may also make recommendations to the Safety Officer for additional data review should a concern arise. The Safety Officer may suggest appropriate courses of action to address general study safety issues which may arise. If warranted, the Safety Officer may recommend at any time that the entire protocol be suspended temporarily or terminated permanently. These recommendations, containing fully blinded information, will be directed to the investigator, the IRBMED and Genentech which has the responsibility to accept, reject or modify the Safety Officer's recommendations. The Safety Officer may also review medical record information, as needed.

12. STUDY CLOSEOUT

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech and IRBMED This includes all the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

13. REFERENCES

1. Meyer KC, Raghu G, Verleden GM, Corris PA, Aurora P, Wilson KC, Brozek J, Glanville AR, the IATSERSBOSTFC, the IATSERSBOSTFC. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *The European respiratory journal* 2014; 44: 1479-1503.
2. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2014; 33: 127-133.
3. Sato M, Waddell TK, Wagnetz U, Roberts HC, Hwang DM, Haroon A, Wagnetz D, Chaparro C, Singer LG, Hutcheon MA, Keshavjee S. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2011; 30: 735-742.
4. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE, Jr., Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM, Group CS. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377: 1760-1769.
5. 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, Group AS. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *The New England journal of medicine* 2014; 370: 2083-2092.
6. Burgel PR, Bergeron A, de Blic J, Bonniaud P, Bourdin A, Chanez P, Chinet T, Dalphin JC, Devillier P, Deschildre A, Didier A, Kambouchner M, Knoop C, Laurent F, Nunes H, Perez T, Roche N, Tillie-Leblond I, Dusser D. Small airways diseases, excluding asthma and COPD: an overview. *European respiratory review : an official journal of the European Respiratory Society* 2013; 22: 131-147.
7. Galban CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, Galban S, Rehemtulla A, Kazerooni EA, Martinez FJ, Ross BD. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nature medicine* 2012; 18: 1711-1715.
8. Verleden SE, Vos R, Vandermeulen E, Ruttens D, Bellon H, Heigl T, Van Raemdonck DE, Verleden GM, Lama V, Ross BD, Galban CJ, Vanaudenaerde BM. Parametric Response Mapping of Bronchiolitis Obliterans Syndrome Progression After Lung Transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2016.
9. Belloli EA, Degtiar I, Wang X, Yanik GA, Stuckey LJ, Verleden SE, Kazerooni EA, Ross BD, Murray S, Galban CJ, Lama VN. Parametric Response Mapping as an Imaging Biomarker in Lung Transplant Recipients. *American journal of respiratory and critical care medicine* 2016.
10. Belloli EA, Wang X, Murray S, Forrester G, Weyhing A, Lin J, Ojo T, Lama VN. Longitudinal Forced Vital Capacity Monitoring as a Prognostic Adjunct after Lung Transplantation. *American journal of respiratory and critical care medicine* 2015.
11. Lama VN, Smith L, Badri L, Flint A, Andrei AC, Murray S, Wang Z, Liao H, Toews GB, Krebsbach PH, Peters-Golden M, Pinsky DJ, Martinez FJ, Thannickal VJ. Evidence for tissue-resident mesenchymal stem cells in human adult lung from studies of transplanted allografts. *The Journal of clinical investigation* 2007; 117: 989-996.
12. Badri L, Murray S, Liu LX, Walker NM, Flint A, Wadhwa A, Chan KM, Toews GB, Pinsky DJ, Martinez FJ, Lama VN. Mesenchymal stromal cells in bronchoalveolar lavage as

predictors of bronchiolitis obliterans syndrome. *American journal of respiratory and critical care medicine* 2011; 183: 1062-1070.