AIDA VENADO, PI

Clinical Research Protocol

PIRFENIDONE FOR RESTRICTIVE CHRONIC LUNG ALLOGRAFT DYSFUNCTION (PIRCLAD)

Protocol Number:	IRB study number 16-20710
Version Date:	May 8, 2020
Investigational Product:	None
IND Number:	N/A
Development Phase:	N/A
Sponsor:	Aida Venado (PI) 500 Parnassus Avenue MUW 420 Box 0115 San Francisco, CA 94143-2203
Funding Organization:	Nina Ireland program for Lung Health discretionary funds from Dr. Jeffrey Golden
Principal Investigator:	Name: Aida Venado Telephone: 404-983-5704 Fax: E-mail: aida.venado@ucsf.edu
Medical Monitor:	Name: Leah Witt, MD Telephone: Fax: E-mail: leah.witt@ucsf.edu
Coordinating Center:	

Approval:

PI or Sponsor Signature (Name and Title) *Date*

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the sponsor with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number:

Protocol Title: **PIRFENIDONE FOR RESTRICTIVE ALLOGRAFT DYSFUNCTION (PIRCLAD)**

Protocol Date: May 8, 2020

Investigator Signature	*Date*

Print Name and Title

Site # _____

Site Name UCSF

Address *500 Parnassus Avenue*

MUW 420, Box 0115

San Francisco, CA 94143

Phone Number *404-983-5704*

PROTOCOL SYNOPSIS

TITLE	**PIRFENIDONE FOR RESTRICTIVE ALLOGRAFT DYSFUNCTION (PIRCLAD)**
SPONSOR	Nina Ireland Program for Lung Health discretionary funds from Dr. Jeffrey Golden
FUNDING ORGANIZATION	UCSF
NUMBER OF SITES	1
RATIONALE	Long-term survival after lung transplant is limited by the development of chronic lung allograft dysfunction. In approximately 30% of cases, chronic lung allograft dysfunction has a restrictive phenotype (RCLAD) characterized by fibrosis with rapid progression. Approximately 60% of patients with RCLAD die within one year from respiratory failure. Currently, there are no therapies available for RCLAD. Due to the similarities between RCLAD and Idiopathic Pulmonary Fibrosis (IPF), there is keen interest in the transplant community to investigate the effect of the anti-fibrotic drug pirfenidone in RCLAD. Pirfenidone has been proved to slow the progression of IPF and is approved by the Food and Drug Administration (FDA) for that indication. This protocol will evaluate the safety and tolerability of pirfenidone in lung transplant recipients with RCLAD. The results of this pilot study will provide the foundation for a multicenter randomized control trial to evaluate the efficacy of pirfenidone in slowing the progression of RCLAD.
STUDY DESIGN	Interventional, open-label, pilot study
PRIMARY OBJECTIVE	Asses the safety and tolerability of Pirfenidone in lung transplant recipients with RCLAD.
NUMBER OF SUBJECTS	10
SUBJECT SELECTION CRITERIA	Inclusion Criteria: Subjects aged 18 to 80 years old, who underwent bilateral lung transplantation at UCSF and have a diagnosis of RCLAD based on the International Heart and Lung Transplant (ISHLT) classification. The diagnosis of RCLAD is based on spirometry (FEV1 ≤ 80% and FVC ≤ 80% of best post-transplant baseline) and CT scan (e.g. pleuroparenchymal fibroelastosis) findings. Subjects with steady-state blood concentration of tacrolimus, as

	assessed by 10-12 hour trough level. Exclusion Criteria: Patients with RCLAD will be excluded if they are, in the judgment of the investigator, unlikely to tolerate pirfenidone. Other exclusion criteria will include: • FVC decline related to non-RCLAD causes (e.g. pulmonary edema, pleural effusion, etc). • Patients with any severe comorbidity complicating RCLAD which might determine their prognosis and functional level (e.g. active malignant disease) within the last 12 months. • Patients who have resumed smoking after transplantation. • Renal insufficiency (creatinine clearance < 30 ml/min calculated by the CKD-Epi formula). • Total bilirubin above the upper limit of the normal range (ULN), except in patients with predominantly unconjugated hyperbilirubinemia (e. g. Gilbert's disease). • Aspartate or alanine aminotransferase (AST or ALT) > 3 times the ULN. • Known allergy of hypersensitivity to Pirfenidone • Ongoing use or expected use of any of the following therapies: - Strong inhibitors of CYP1A2 (e.g. fluvoxamine or enoxacin). - Moderate inhibitors of CAYP1A2 (e. g. mexiletine, thiabendazole, or phenylpropanolamine). Ciprofloxacin will be allowed only at doses equal or less than 500 mg BID. • Inability to provide informed consent.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Pirfenidone 2403 mg/day for 56 weeks. Pirfenidone dose will be titrated up as follows: 801 mg/day (1 capsule, 3 times daily) for 2 weeks, then 1602 mg/day (2 capsules, 3 times daily) for 2 weeks, then 2403 mg/day (3 capsules, 3 times daily) for 52 weeks.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	N/A

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be in the study for 56 weeks. Subjects that wish to continue taking pirfenidone beyond 56 weeks may be eligible for PIRCLAD extension until September 30, 2021. The Principal Investigator will determine eligibility for PIRCLAD extension on a case by case basis. Subjects must continue to meet the inclusion and exclusion criteria, and continue monitoring with laboratory tests, study coordinator calls, clinic visits, pulmonary function tests, and CT scan imaging. The total duration of the study is expected to be up to 48 months. Fifteen months will be for subject recruitment and an additional 14 months for subject follow-up. Subjects eligible for PIRCLAD extension will have up to 19 months of follow up. The last study coordinator call will be 28 days after the last pirfenidone dose.
CONCOMMITANT MEDICATIONS	Patients will continue their current immunosuppression regimen consisting of prednisone, mofetil mycophenolate, tacrolimus and sirolimus. Strong inhibitors of CYP1A2 (e.g. fluvoxamine or enoxacin) and moderate inhibitors of CYP1A2 (e. g. mexiletine, thiabendazole, or phenylpropanolamine) will not be allowed. Ciprofloxacin will be allowed only at doses equal or less than 500 mg twice daily.
SAFETY EVALUATIONS **(PRIMARY OUTCOMES)**	Tolerability of pirfenidone: The primary outcome will be the number of subjects that discontinue pirfenidone due to a treatment emergent adverse event (TEAE). A secondary outcome will be the proportion of subjects experiencing a TEAE. Tacrolimus dose change: The outcome will be the ratio of tacrolimus-on-pirfenidone to tacrolimus-off-pirfenidone corrected for the subject's specific steady-state tacrolimus concentration. Subjects with steady-state blood concentration of tacrolimus, as assessed by 10-12 hour trough level, will initiate pirfenidone. Tacrolimus trough level will be measured weekly for the first 6 weeks after starting pirfenidone. Another measurement will be done at week 8. Once a therapeutic blood concentration (8-12 ng/ml) is achieved, measurements will be done monthly. First, we will calculate the concentration-to-dose ratio of tacrolimus on and off pirfenidone by dividing the tacrolimus blood concentration by the corresponding total daily dose of tacrolimus for each period. To obtain the conversion ratio, then we will divide the concentration-to-dose ratio for tacrolimus-on-pirfenidone by the concentration-to-dose ratio for tacrolimus-off-pirfenidone ([blood concentration on pirfenidone/daily dose on pirfenidone]/[blood concentration off pirfenidone/daily dose off pirfenidone]).
EFFICACY EVALUATIONS	FVC decline: We will evaluate change in FVC every 3 months after initiation of pirfenidone.

(SECONDARY OUTCOMES)	Radiographic progression: We will evaluate fibrosis scores on chest CT at RCLAD onset and in the follow up CT scans performed as part of routine clinical care.
PLANNED INTERIM ANALYSES	Quarterly
Rationale for Number of Subjects	This is a pilot study with the primary outcome of determining pirfenidone tolerability and its effect on tacrolimus dosing. Even with a small cohort, we hypothesize we will be powered to detect a significance difference in tacrolimus dosing. Based on the single report of tacrolimus dosing increase of 2.5 fold, and conservatively estimating a standardized effect size of 1 (doubling of tacrolimus dose and a standard deviation of the change of 50%), a sample of 8 subjects would be required to detect a significant difference, assuming a two-sided α of 0.05 and β of 0.20**.**

1 BACKGROUND

Despite advances in lung transplantation, median survival remains only 55% at 5 years.[1] The primary cause of death is chronic lung allograft dysfunction (CLAD), occurring in 43% of recipients at 5 years.[1] Recently, it has been recognized that CLAD can have an obstructive (BOS) or a restrictive (RCLAD) phenotype, also known as restrictive allograft syndrome (RAS), and that both may coexist.[2,3] These phenotypes differ not only in their spirometric, radiographic[4] and histologic [5,6] features but also in their rates of progression[7] and survival[8-13] (Figure 1). Thus, there is a critical need to find therapies other than re-transplantation, which remains the only effective therapeutic option and explore the pathobiology driving RCLAD.[14]

RCLAD shares features with Idiopathic Pulmonary Fibrosis (IPF), including its progressive and lethal course, extracellular matrix deposition, architectural distortion, fibroblast proliferation[15], and short telomeres in lung epithelial cells[16] (Fig 2). These common features suggest RCLAD and IPF may share molecular pathogenesis. As a result, some have explored using FDA approved anti-fibrotic medications for IPF in RCLAD in case reports.[17,18]

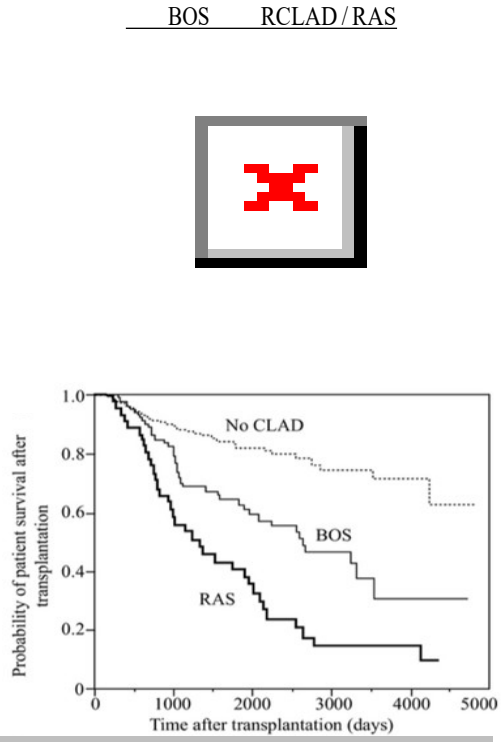


Fig 1. Restrictive Allograft syndrome (RAS). 3.

2 STUDY RATIONALE

This proposal aims to gather the preliminary data needed to design a multicenter randomized controlled trial (RCT) of pirfenidone for RCLAD. To do so, we first need evidence of tolerability, to understand drug interactions with the immunosuppressive regimen used to maintain allograft function and early evidence that pirfenidone may slow FVC decline and radiographic progression in RCLAD.

Evidence that pirfenidone is well tolerated in transplant recipients and that it slows the progression of RCLAD would be paradigm shifting. Further, identifying subjects at risk for RCLAD before the onset of spirometric changes would allow to start therapeutic interventions sooner, maximizing their benefit. Finding biomarkers that predict response to pirfenidone would identify patients most likely to benefit.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives of this proposal are to assess tolerability of pirfenidone and determine its impact on tacrolimus blood concentration.

We hypothesize that treatment-emergent adverse effects (TEAE) in lung transplant recipients will be similar to subjects with IPF, leading to drug discontinuation in the same proportion of subjects.[19]

Based on available literature, we hypothesize that initiation of pirfenidone will be associated with an increase in tacrolimus dose.[17]

3.2 Secondary Objectives

To determine if pirfenidone slows allograft dysfunction in RCLAD as evidenced by a slower FVC decline and/or a slower progression of radiographic findings.

4 STUDY DESIGN

4.1 Study Overview

1) We will screen for eligible subjects using the computer algorithm on spirometry data abstracted from Apex monthly and by suggestion of the transplant pulmonologists. 2) Then, we will review CT scans to adjudicate a diagnosis of RCLAD. 3) Finally, our pharmacist will determine if tacrolimus dose is stable. After these 3 steps are completed subjects will be eligible for the study.

Subjects will be recruited at their transplant clinic visit or by phone if they previously consented to be contacted with new research study opportunities. We will seek to enroll ten subjects, who will receive pirfenidone for 52 weeks, titrated to 2403 mg/day (3 capsules, 3× daily) over a period of six weeks. [20] Genentech has agreed to provide study drug free of cost.

TEAE will be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0[21]. Our study coordinator will contact subjects by phone every 2 weeks for the first 6 weeks to inquire about TEAE and then monthly. Subjects will be provided a phone number to report any additional TEAE. A Data Safety Monitoring Board will be convened.

As part of their routine post-transplant surveillance, subjects have monthly laboratory testing that includes tacrolimus blood concentration and liver function tests. Therefore, the manufacturer recommendations of monitoring liver function tests monthly for the first six months and then every 3 months while taking Pirfenidone, will be followed.

Subjects will continue their routine care with clinic visits, spirometry and CT as clinically indicated. In our clinical practice, subjects with RCLAD are expected to have a clinic visit and spirometry approximately every 3 months and a CT scan every 6 to 12 months.

If RCLAD subjects in the study undergo bronchoscopy for a clinical indication, bronchoalveolar lavage, biopsies, airway brushes and plasma specimens will be collected in the biorepository for future analysis of changes in pro-fibrotic mediators after initiation of pirfenidone. These specimens will be collected as part of the ongoing "Lung Transplantation: Improving outcomes through the development of a clinical database and biorepository" study number 13-10738. In the future, we plan to explore whether subjects with RCLAD have a greater rate of decline in telomere length in airway epithelial cells compared subjects without RCLAD.

5 SUBJECT SELECTION

5.1 Study Population

Subjects with a diagnosis of RCLAD who meet the inclusion and exclusion criteria will be eligible for participation in this study.

5.2 Inclusion Criteria

1. Subjects aged 18 to 80 years old who underwent bilateral lung transplantation at UCSF.

2. Diagnosis of RCLAD based on the International Heart and Lung Transplant (ISHLT) classification. The diagnosis of RCLAD is based on spirometry (FEV1 ≤ 80% and FVC ≤ 80% of best post-transplant baseline) and CT scan (e.g. pleuroparenchymal fibroelastosis) findings.

3. Subjects with steady-state blood concentration of tacrolimus, as assessed by 10-12 hour trough level.

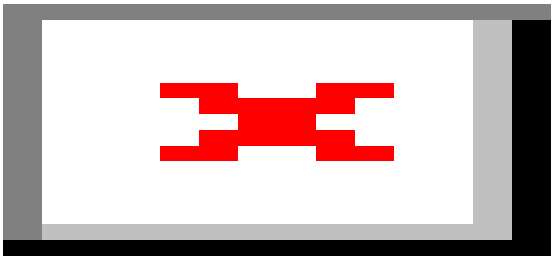
5.3 Exclusion Criteria

Patients with RCLAD will be excluded if they are, in the judgment of the investigator, unlikely to tolerate pirfenidone. Other exclusion criteria will include:

1. FVC decline related to non-RCLAD causes (e.g. pulmonary edema, pleural effusion, etc).
2. Patients with any severe comorbidity complicating RCLAD which might determine their prognosis and functional level (e.g. active malignant disease) within the last 12 months.
3. Patients who have resumed smoking after transplantation.
4. Renal insufficiency (creatinine clearance < 30 ml/min calculated by the CKD-Epi formula).
5. Total bilirubin above the upper limit of the normal range (ULN)
6. Aspartate or alanine aminotransferase (AST or ALT) > 3 times the ULN.
7. Known allergy of hypersensitivity to Pirfenidone
8. Ongoing use or expected use of any of the following therapies:
    - Strong inhibitors of CYP1A2 (e.g. fluvoxamine or enoxacin).
    - Moderate inhibitors of CAYP1A2 (e. g. mexiletine, thiabendazole, or phenylpropanolamine). Ciprofloxacin will be allowed only at doses equal or less than 500 mg BID.
9. Inability to provide informed consent.

6 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed below.



Week	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	56	57	60
Start Pirfenidone	x																				
Study coordinator call		x		x		x		x	x	x	x	x	x	x	x	x	x	x	x		x
Tacrolimus level	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Liver function tests				x			x	x	x	x	x			x			x				
Clinic visit								x			x			x			x				
FVC measure								x			x			x			x				
CT scan	x																				
Stop Pirfenidone																				x	

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject.

Any clinically significant findings will be communicated to the patients and, with their consent, to the patients' clinical providers.

Study coordinator call: Our study coordinator will contact subjects by phone every 2 weeks for the first 6 weeks to inquire about treatment-emergent adverse events (TEAE) and then monthly. TEAE will be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0[21]. The last phone call will be 28 days after the last pirfenidone dose. Subjects will be provided a phone number to report any additional TEAE. A Data Safety Monitoring Board will be convened.

Tacrolimus concentration measurement: Patients will continue to use their chosen laboratory for tacrolimus measurement, as part of their clinical care. As it is our clinical practice, the results will be reviewed daily through Titus and the transplant nurse coordinators will contact the patients with instructions to adjust their tacrolimus dose.

Liver function test measurement: Patients will continue to use their chosen laboratory for monthly liver function test measurement according to the post-transplant surveillance protocol. We will track these values every month for the first 6 months of Pirfenidone therapy and every 3 months for the remaining 6 months, following manufacturer's recommendations.

Office spirometry (FVC): As part of their clinical care, patients will have office FVC measurement (spirometry) approximately every 3 months or more often if clinically indicated according to ATS/ERS guidelines.

High-resolution chest CT (HRCT): Patients will have a HRCT every 6 to 12 months as part of their clinical care. We will review these images to evaluate fibrosis scores.

Reporting of clinical events: All patients will be asked to report clinical events (e.g. new or worsening symptoms, unscheduled medical visits, hospitalizations) to the study coordinator over the phone. The study coordinator will ask the transplant nurse coordinators and review the medical record to investigate if any other events occurred.

Protocol Amendment

Subjects that wish to continue taking pirfenidone beyond 56 weeks may be eligible for PIRCLAD extension for up to 76 weeks. The Principal Investigator will determine eligibility for PIRCLAD extension after reviewing the 52-week study coordinator call. Subjects must continue to meet the original inclusion and exclusion criteria. Subjects will continue to be monitored per study protocol (laboratory tests, study coordinator calls, clinic visits, pulmonary function tests, and CT scan imaging) as long as they remain on pirfenidone. The last pirfenidone dose will be on September 30, 2021. The last study coordinator call will occur 28 days after the last pirfenidone dose. Reporting of adverse events and protocol violations for these subjects will remain the same. The duration of PIRCLAD extension is diagrammed below.

Week	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120	124	128	129	132
Continue Pirfenidone	x																				
Study coordinator call	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Tacrolimus level	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Liver function tests	x			x			x			x			x			x			x		
Clinic visit	x			x			x			x			x			x			x		
FVC measure	x			x			x			x			x			x			x		
CT scan	x																				
Stop Pirfenidone																				x	

7 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed.

8 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

Interim analysis plans: We will plan interim analyses of data quality and patient compliance on a quarterly basis to insure adequate study conduct. Modifications to the study conduct (e.g. changes to the outcome measures, or even cessation of the study if indicated by issues with performance or outcomes) will be considered at each of these analyses.

Power: This is a pilot study with the primary outcome of determining pirfenidone tolerability and its effect on tacrolimus dosing. Even with a small cohort, we hypothesize we will be powered to detect a significance difference in tacrolimus dosing. Based on the single report of tacrolimus dosing increase of 2.5 fold, and conservatively estimating a standardized effect size of 1 (doubling of tacrolimus dose and a standard deviation of the

change of 50%), a sample of 8 subjects would be required to detect a significant difference, assuming a two-sided α of 0.05 and β of 0.20.

Data analysis plan: Since we will be comparing within subject changes, we will use paired t-test to compare the tacrolimus-on-pirfenidone to tacrolimus-off-pirfenidone ratio. For analyses involving repeated measures including change in FVC, fibrosis score, and telomere length, we will use mixed effects models[22] including subject as a fixed effect.
Slopes before and after the initiation of pirfenidone will be compared.

9 DATA COLLECTION, RETENTION AND MONITORING

9.1 Data Collection and Management

Data will be collected on paper worksheets and entered into the Research Electronic Data Capture (REDCap) system by dedicated clinical research coordinators using study-specific clinical research forms. REDCap is an easy-to-use highly secure data management system provided by UCSF to investigators for research use at no charge. All REDCap data will be reviewed and cleaned by the study investigators after data entry. Paper worksheets will be kept in patient binders as backup and securely stored.

9.2 Availability and Retention of Investigational Records

The Investigator will make study data accessible to the IRB, and other interested parties upon request. A file for each subject must be maintained that includes the signed Informed Consent and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived. All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years.

9.3 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs.

10 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as legally required. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

10.1 Protocol Amendments

Protocol amendments will not be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

10.2 Institutional Review Boards

The protocol and consent form will be reviewed and approved by the IRB at UCSF prior to study initiation. Serious adverse experiences will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form and HIPAA authorization prior to submission to the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If

appropriate and required by the local IRB, assent from the subject will also be obtained. A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records.

10.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by the investigators. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

A publication will be done at the end of the 52-week trial, and a separate publication will potentially be done at the end of the extension phase of trial.

10.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
5. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection when required.
6. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
7. Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others.
8. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
9. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

11 SAFETY REPORTING OF ADVERSE EVENTS

11.1 Assessment of Safety

11.1.1 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.

11.1.2 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 RCLAD 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.

11.1.3 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 (IND Safety Reports).

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 study treatment and ends 28 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 Pirfenidone (see following guidance), and actions taken.

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

11.2.3 Yes

There is a plausible temporal relationship between the onset of the AE and administration of Pirfenidone, 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 Pirfenidone; and/or the AE abates or resolves upon discontinuation of Pirfenidone or dose reduction and, if applicable, reappears upon re-challenge.

11.2.4 No

Evidence exists that the AE has an etiology other than Pirfenidone (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to Pirfenidone 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.

11.3.2.1 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.

11.3.2.2 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".

11.3.2.3 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").

11.3.2.4 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.

11.3.2.5 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

11.3.2.6 e. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 28 days after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within *28 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 Pirfenidone should be reported as an SAE.

11.3.2.7 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 Pirfenidone 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/CTV

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.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

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'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Sponsor (UCSF) to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

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.

Pirfenidone Events of Special Interest are:

Hys and Stiamp:

1.Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.

- Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN
- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- There is a risk of pirfenidone causing elevation in liver function tests. ALT, AST, and bilirubin elevations have occurred with pirfenidone including cases of drug-induced liver injury. In the postmarketing setting, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcomes, have been reported.

2.Suspected transmission of an infectious agent by the study drug, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

11.3.2.8 I.Adverse Event Reporting

UCSF will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

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

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to

Fax:650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

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 Roche 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 Roche within fifteen (15) calendar days of the awareness date.

- **Other SAEs**

  Serious AE reports that are unrelated to the Product shall be transmitted to Roche 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 Roche 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.

  Pregnancies in Female Partners of Male Patients

  Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date

- **AESIs**

  AESIs requiring expedited reporting shall be forwarded to Roche within fifteen (15) calendar days of the awareness date. Others shall be sent within thirty (30) calendar days.

- **Non-serious AEs**

  Non-serious AEs shall be transmitted to Roche on a periodic (e.g., monthly) line-listing containing the following elements (Protocol number, Patient ID, Patient birth date, Adverse Event/MedDRA term, Seriousness of event, Onset date of event, Death date, Product received, Date of first dose, Cause(s) of event, Adverse Event description).

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

Special situation reports

In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Roche 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)

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

- **Product Complaints**
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

REPORTING TO REGULATORY AUTHORITIES, ETHICS COMMITTEES AND INVESTIGATORS

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

UCSF, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

UCSF will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

j. Aggregate Reports

Development Safety Update Report

Sponsor as the Sponsor of the Study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. *Sponsor* agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.

Genentech agrees to forward to *Sponsor* an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that Sponsor may cross-reference the executive summary of the Genentech/Roche DSUR, as applicable.

Other Reports:

UCSF will forward a copy of the Publication to Roche upon completion of the Study.

Note: Investigators should also report events to their IRB as required.

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

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

11.3.3 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

11.3.3.1 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/media/69876/download

11.4 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and 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:

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by *Genentech.* However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. *Genentech* agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. *Genentech*

agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

Data and Safety Monitoring Plan (required by the UCSF IRB)

DATA REVIEW

Investigators (Dr. Venado and Dr. Dewey) will conduct continuous review of data from UCSF enrolled patient safety at monthly study group meetings where the results of each patient's treatment are discussed. The discussion will include the number of patients, significant toxicities as described in the protocol, doses adjustments, and observed responses. The research team will adhere to the UCSF IRB reporting requirements.

INTERIM ANALYSIS

Interim analyses will be discussed quarterly with Dr. Leah Witt, who will serve as the Medical Monitor to assess safety. Enrollment will continue except if there were unexpected toxicities. These evaluations will not be assessed by any formal statistical test, only listings and summary estimates will be provided. The results of interim analyses will be documented and assessed internally by the study core team. Written letters will be submitted to the IRB and the investigators as necessary.

STOPPING RULES

On section 5.4.2.1 "Overview of Adverse Events" of the Investigator's Brochure provided by Genentech it states that almost every patient in both the pirfenidone and placebo treatment groups experienced an adverse event (AE) (99% and 97.9%, respectively). A total of 42.7% of patients in the pirfenidone treatment group had an AE that led to a dose reduction or interruption of any duration compared to 16.2% of patients in the placebo groups; a much lower percentage discontinued treatment early (14.6%) due to any AE. Overall 71 patients died. Fewer patients died in the pirfenidone group than in the placebo group (27 patients, 4.3% vs 44 patients, 7.1%). The treatment group difference was driven in part by a reduction in deaths due to IPF in the pirfenidone-treated patients (10 patients, 1.6% vs 21 patients, 3.4%). On section 5.4.2.5 "Adverse Events Leading to Early Discontinuation of Study Treatment" it states that 14.6% of subjects discontinued treatment due to an AE in the pirfenidone group, compared to 9.6% in the placebo group. Most patients discontinued the treatment in the first year.

Our null hypothesis is that tolerability of pirfenidone in the PIRCLAD study will be similar to that in the PIPF-004, PIPF-006 (CAPACITY), and PIPF-016 (ASCEND) studies. Therefore, we expect the proportion of subjects enrolled in the PIRCLAD study will be similar pirfenidone early due to an AE will be the same or lower. Given the small sample size of the PIRCLAD study, we calculated the maximum early discontinuation proportion that would be similar to 14.6% considering a $p<0.05$ for statistical significance. This proportion is 25% of study participants ($p=0.0451$), which would be consistent with the findings of the PASSPORT study. The PASSPORT study, a multicenter, prospective, observational post-authorization study that evaluated long-term safety of pirfenidone found that in real-world practice, AE lead to pirfenidone discontinuation in 28.7% (290/1009) of patients, after a median of 99.5 days[23].

Thus, we expect that up to 3 of the 10 subjects in the study will discontinue pirfenidone early due to an AE.
The PIRCLAD study will stop enrolling new participants if more than 3 subjects discontinue pirfenidone early due to an AE.
Participants who are tolerating pirfenidone well and wish to continue taking it will be allowed to remain in the PIRCLAD study.

Discontinuation:
Patients may temporarily suspend all study drugs for up to 28 consecutive days if they experience toxicity that is considered related to study treatment and that requires a study

treatment hold. Patients who miss > 28 consecutive days of scheduled study treatment because of drug-related adverse events will be discontinued from the study. Exceptions may be made after discussions with the investigators, approval by the Medical Monitor, and consistency with the regulations of the Institutional Review Board/Ethics Committee (IRB/EC).

Patients who miss 14 or more days of Pirfenidone should reinitiate treatment by undergoing the initial 4 week titration regimen up to the full maintenance dosage. For treatment interruption of less than 14 days, the dosage prior to the interruption can be resumed.

DOSE MODIFICATIONS
Dose-reduction Procedure for Adverse Event Management:

If patients experience significant adverse reactions (i.e., gastrointestinal, photosensitivity reaction or rash), they will have the following temporary dose reduction: reduce dose to 267 mg three times daily (801 mg/day) for 14 days, followed by 534 mg three times daily (1602 mg/day) for another 14 days, prior to returning to the protocol dose of 801 mg three times daily (2403 mg/day). If adverse reactions do not resolve with reducing dose to 267 mg three times daily (801 mg/day) for 14 days, patients will discontinue pirfenidone for 14 days. Any return to protocol dose level after dose reduction must follow documentation of resolution of the adverse event and after discussion with the medical monitor.

If a patient exhibits 2-3 times the upper limit of normal (ULN) ALT and/or AST elevation without symptoms or hyperbilirubinemia after starting Pirfenidone therapy, he/she will discontinue Pirfenidone for 14 days and reinitiate treatment by undergoing the initial 4-week titration regimen up to the full maintenance dosage if tolerated and repeat liver chemistry tests are within normal limits. We will exclude other causes, monitor the patient closely, and repeat liver chemistry tests as clinically indicated.
If a patient exhibits >3 times ULN ALT and/or AST elevation he/she will permanently discontinue Pirfenidone and will not be re-challenged with it.
Dosage Modification due to Drug Interactions
Strong CYP1A2 Inhibitors (e.g., fluvoxamine, enoxacin): Reduce Pirfenidone to 267 mg three times a day (801 mg/day).
Moderate CYP1A2 Inhibitors (e.g., ciprofloxacin) With use of ciprofloxacin at a dosage of 750 mg twice daily, patients will reduce Pirfenidone to 534 mg three times a day (1602 mg/day).

WITHDRAWAL
Discontinuation of Patients:

The investigator will discontinue patients from the study drug or the study or both in the following circumstances:

- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

- The investigator decides that the patient should be withdrawn from the study. If a serious adverse event or a clinically significant laboratory value is the basis for this decision, the investigator will discontinue the study therapy and take appropriate measures. The investigator must **immediately** notify the study sponsor or its designee.
- The patient or attending physician requests withdrawal of the patient from the study.
- The investigator or the study sponsor stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- The study therapies have shown unacceptable toxicity.
- The patient becomes pregnant or fails to use adequate birth control (for women with reproductive potential).
- The patient is noncompliant with study procedures.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document.

Study agents assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

References

1. Valapour M, Skeans MA, Smith JM, et al. Lung. *Am J Transplant.* Jan 2016;16 Suppl 2:141-168.

2. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant.* Feb 2014;33(2):127-133.

3. Verleden SE, Ruttens D, Vandermeulen E, et al. Restrictive chronic lung allograft dysfunction: Where are we now? *J Heart Lung Transplant.* May 2015;34(5):625-630.

4. Saito T, Horie M, Sato M, et al. Low-dose computed tomography volumetry for subtyping chronic lung allograft dysfunction. *J Heart Lung Transplant.* Jan 2016;35(1):59-66.

5. Pakhale SS, Hadjiliadis D, Howell DN, et al. Upper lobe fibrosis: a novel manifestation of chronic allograft dysfunction in lung transplantation. *J Heart Lung Transplant.* Sep 2005;24(9):1260-1268.

6. Ofek E, Sato M, Saito T, et al. Restrictive allograft syndrome post lung transplantation is characterized by pleuroparenchymal fibroelastosis. *Mod Pathol.* Mar 2013;26(3):350-356.

7. Sato M, Hwang DM, Waddell TK, Singer LG, Keshavjee S. Progression pattern of restrictive allograft syndrome after lung transplantation. *J Heart Lung Transplant.* Jan 2013;32(1):23-30.

8. Sato M, Waddell TK, Wagnetz U, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. *J Heart Lung Transplant.* Jul 2011;30(7):735-742.

9. Todd JL, Jain R, Pavlisko EN, et al. Impact of forced vital capacity loss on survival after the onset of chronic lung allograft dysfunction. *Am J Respir Crit Care Med.* Jan 15 2014;189(2):159-166.

10. Verleden SE, de Jong PA, Ruttens D, et al. Functional and computed tomographic evolution and survival of restrictive allograft syndrome after lung transplantation. *J Heart Lung Transplant.* Mar 2014;33(3):270-277.

11. Verleden GM, Vos R, Verleden SE, et al. Survival determinants in lung transplant patients with chronic allograft dysfunction. *Transplantation.* Sep 27 2011;92(6):703-708.

12. Woodrow JP, Shlobin OA, Barnett SD, Burton N, Nathan SD. Comparison of bronchiolitis obliterans syndrome to other forms of chronic lung allograft dysfunction after lung transplantation. *J Heart Lung Transplant.* Oct 2010;29(10):1159-1164.

13. Verleden SE, Ruttens D, Vandermeulen E, et al. Predictors of survival in restrictive chronic lung allograft dysfunction after lung transplantation. *J Heart Lung Transplant.* Apr 16 2016.

14. Verleden SE, Todd JL, Sato M, et al. Impact of CLAD Phenotype on Survival After Lung Retransplantation: A Multicenter Study. *Am J Transplant.* Aug 2015;15(8):2223-2230.

15. Fernandez IE, Heinzelmann K, Verleden S, Eickelberg O. Characteristic patterns in the fibrotic lung. Comparing idiopathic pulmonary fibrosis with chronic lung allograft dysfunction. *Ann Am Thorac Soc.* Mar 2015;12 Suppl 1:S34-41.

16. Alder JK, Chen JJ, Lancaster L, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. *Proc Natl Acad Sci U S A.* Sep 2 2008;105(35):13051-13056.

17. Vos R, Verleden SE, Ruttens D, et al. Pirfenidone: a potential new therapy for restrictive allograft syndrome? *Am J Transplant.* Nov 2013;13(11):3035-3040.

18. Suhling H, Bollmann B, Gottlieb J. Nintedanib in restrictive chronic lung allograft dysfunction after lung transplantation. *J Heart Lung Transplant.* Feb 9 2016.

19. Lancaster L, Albera C, Bradford WZ, et al. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. *BMJ Open Respir Res.* 2016;3(1):e000105.

20. Khanna D, Albera C, Fischer A, et al. An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial. *J Rheumatol.* Sep 2016;43(9):1672-1679.

21. Cancer Therapy Evaluation Program. 2003. Common terminology criteria for adverse events, version 3.0 (CTCAE). DCTD, NCI, NIH, DHHS: March 31, 2003. (http://ctep.cancer.gov). Publication date: December 12, 2003.

22. Pinheiro JC BD. *Mixed-Effects Models in S and S-Plus.* New York: Springer-Verlag; 2000.

23. Cottin V, Koschel D, Günther A, et al. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. *ERJ Open Res.*

Oct 2018;4(4).