INVESTIGATOR INITIATED STUDY (ML29875)
ClinicalTrials.gov: NCT02958917

PROTOCOL TITLE:
A Randomized, Double-Blind, Placebo-Controlled, Study of the Efficacy and Safety of Pirfenidone in Patients with Fibrotic Hypersensitivity Pneumonitis

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BACKGROUND INFORMATION

Hypersensitivity pneumonitis (HP) is an immunologically mediated form of interstitial lung disease (ILD), in response to inhalation exposure to a large variety of antigens, of varying intensity, clinical presentation and natural history.[1]

In the USA, the one-year prevalence rates for HP range from 1.39 to 2.06 cases per 100,000 persons and incidence rates range from 0.82 to 1.74 cases per 100,000. The prevalence and incidence of HP increased with age. Among adults aged 65 and over, prevalence rates range from 3.63-6.57 cases per 100,000 persons and incidence rates range from 2.41-5.18 cases per 100,000.[2]

A subgroup of patients with HP develops fibrotic HP (FHP), characterized clinically by ventilatory restriction and the presence of chest imaging or pathologic evidence of lung fibrosis.[3] FHP is an irreversible and often progressive disease that distorts the lung architecture and ultimately results in hypoxemia and respiratory failure. The presence of lung fibrosis on HRCT scans and/or in surgical lung biopsy specimens is the strongest predictor of death.[4-8] When fibrosis is present, the median survival time may be similar to those with IPF (4.9 years; 95% CI, 2.9-7.5).[4] Indeed, FHP shares similarities with the most devastating of the ILD, namely IPF. FHP can lead to end-stage pulmonary fibrosis with excessive collagen and extracellular matrix deposition.[3,9,10] Also, IPF and FHP are known to have overlapping clinical manifestations, contributing risk factors (e.g., cigarette smoking, aging)[11] and comorbidities (e.g., pulmonary hypertension),[11,12] histopathologic features[8,13] and prognosis.[11,14] Patients with FHP most commonly present with the insidious onset of progressive exertional dyspnea and a non-productive chronic cough. While patients may encounter periods of clinical, radiologic and functional stability, or slow and gradual progression over many years, others may experience an accelerated decline over months. At any time during the disease course patients may experience acute respiratory exacerbations. These events are unpredictable and sometimes fatal.[15]

Management of FHP is aimed at antigen identification and avoidance. Antigen avoidance can favorably influence FHP survival. Nevertheless, we have shown that even after adjusting for the presence of fibrosis, patient age, pulmonary function and smoking history, survival was shorter for patients with an unidentified inciting antigen (IA) exposure than those with an identified IA exposure (median, 4.88 years vs. 8.75 years),[4] suggesting that pre-existing genetic susceptibility increases the risk of disease progression regardless of the presence or absence of IA.[16] Immunomodulatory therapy, such as corticosteroids and azathioprine is commonly initiated when clinically significant disease progression is recognized. However, it is increasingly clear that traditional immunomodulary therapy (e.g., corticosteroids) does not target key active profibrotic pathways in susceptible FHP patients and that a subset of patients develops a progressive disease phenotype. Results from previous clinical trials suggest that pirfenidone is well tolerated and may slow the decline in or lead to stabilization of pulmonary function in patients with IPF. IPF is a fibrotic lung disease that shares overlapping pathways with FHP. Given the efficacy and safety in previous IPF trials,[17-20]

treatment with pirfenidone may be of value in FHP and should be tested for its clinical efficacy in a well-characterized disease. In an open-label study of 10 patients with pulmonary fibrosis, pirfenidone was well tolerated and no significant adverse effects occurred during one-year treatment when in combination with corticosteroids or azathioprine.[21]
The main goal of the current study is to evaluate the clinical effect of pirfenidone on disease progression and assess the safety and tolerability, in particular when in combination with immunomodulary drugs, among subjects with different severities of FHP.

Description
Pirfenidone is a small non-peptide molecule of low molecular weight (185.2 daltons). Its chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone, and its empirical formula is $C_{12}H_{11}NO$. It is an antifibrotic agent with anti-inflammatory properties. Pirfenidone was approved by European and US regulatory agencies in 2011 and 2014, respectively, for the treatment of IPF.

Potential Benefits and Risks to Human Subjects
The safety of pirfenidone has been characterized in 15 studies involving 1345 subjects and patients; 770 patients have received pirfenidone at a dose of 2403 mg/d or greater. Analyses of this data suggest that the side effects of pirfenidone are readily monitored, typically reversible, and related to tolerability rather than morbidity.
In the LOTUSS study (An Open Label, Randomized, Phase 2 Study of the Safety and Tolerability of Pirfenidone when Administered to Patients with Systemic Sclerosis-Related Interstitial Lung Disease) designed to assess the safety and tolerability of pirfenidone in patients with SSc-ILD at the same therapeutic dose used in IPF, and using 2 dose-titration schedules (4-weeks vs. 2-weeks), with or without stable background systemic sclerosis-ILD therapy; mycophenolate (commonly utilized in HP) was received by 63% of patients in addition to pirfenidone, with similar tolerability to pirfenidone alone. Further, patients who took pirfenidone and mycophenolate, compared with pirfenidone alone, appeared to experience fewer treatment emergent adverse events and discontinuations. A longer dose titration, 4-weeks as opposed to 2-weeks, had more favorable effect on tolerability.[22]
Escalation of dose over the first 4 weeks, dosing with food, use of protection against sun exposure, prompt symptomatic management of intolerance, and monitoring of liver function tests during dosing are recommended to maximize tolerability.

Study Rationale
FHP is a life-threatening and severely debilitating disease. Currently, there is lack of efficacious therapeutic options. Results from four controlled trials,[17-20]suggest that pirfenidone treatment is safe and well tolerated and results in clinically meaningful benefits in a variety of domains, exercise tolerance (change in 6MWT distance), and progression-free survival time in patients with IPF. Given the primacy of loss of lung volumes over time in

patients with FHP, this protocol is intended to confirm that pirfenidone 2403 mg/d reduces decline in %FVC over 52 weeks and that it is safe and tolerable, as observed in the previous IPF studies.

INVESTIGATIONAL PLAN

Objective

- To evaluate the treatment effect of pirfenidone 2403 mg/d compared with placebo on the mean change of percent predicted forced vital capacity (%FVC) in subjects with fibrotic hypersensitivity pneumonitis (FHP).
- To assess the safety and tolerability of pirfenidone at 2403 mg/d when administered to subjects with FHP.

Study design

This is a single-center, randomized, double-blind, placebo-controlled, efficacy and safety study of pirfenidone in subjects with FHP. Approximately 42 subjects will be randomized in a 2:1 ratio to receive pirfenidone 2403 mg/d or placebo for 52 weeks. The primary efficacy endpoint is the mean change in %FVC from Baseline to Week 52, to be analyzed using a rank linear model. Subjects will receive blinded study treatment from the time of randomization until the Week 52 Visit.

Eligible subjects, males and females, aged 18–80 years (inclusive) must have a confident or high-confidence diagnosis of FHP according to pre-specified criteria without evidence of an alternative diagnosis that may contribute to their interstitial lung disease. Subjects will be required to have a FVC ≥40% and DLCO ≥30% at screening.

Subjects will enter the Screening Period, which may last up to 30 days. In addition of brief periods of corticosteroid use for acute FHP exacerbation, subjects will be allowed to receive any other therapy for the treatment of FHP as per pre-specified criteria.

The dose of study treatment will be titrated over 4 weeks (2 weeks at 1 capsule TID; 2 weeks at 2 capsules TID; and 48 weeks at 3 capsules TID (2403 mg/d). Pirfenidone dose modifications or interruption will be allowed for safety or tolerability reasons at any time during the study.

Subjects will have a telephone assessment at Week 1 and 3, and an in-clinic assessment at day 1, weeks 5, 13, 26, 39, and 52. Subjects will be asked to complete an adverse event (AE) and dosing compliance diary between all visits. If subjects discontinue study treatment early for any reason, they will be asked to continue with all scheduled study procedures through Week 52.

A Safety officer will review all deaths and monitor subject safety during the study.

Dose Rationale

Pirfenidone 2403 mg/d was the dose evaluated in the CAPACITY-004, CAPACTIY-006, and ASCEND trials, which demonstrated favorable efficacy, and safety results compared with placebo.

Selection of Study Population
The study population consists of male and female FHP patients aged 18 to 80 years (inclusive) who meet the inclusion and exclusion criteria outlined below.

INCLUSION CRITERIA
Patients must fulfill all of the following criteria to be eligible for enrollment in the study:

*Multidisciplinary Consensus Diagnosis of FHP**

a. Diagnosis of FHP (**figure**), defined from the first instance in which a patient was informed of having FHP for at least 3 to 6 months.
b. Age 18 through 80 years at randomization.
c. Diagnosis of typical or compatible FHP by HRCT according to pre-specified criteria (Note: HRCT scan performed within 4 months of the start of screening may be use if it meets image acquisition guidelines):
    a. Typical FHP: Evidence of lung fibrosis (reticular abnormality and/or, traction bronchiectasis and/or, architectural distortion, and/or honeycombing) with either of the following:
        i. Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones.
        ii. Inspiratory mosaic attenuation with three-density sign.
        AND
        iii. Lack of features suggesting an alternative diagnosis.

    These patients are required to have an identifiable antigen exposure, or an indeterminate or unidentifiable antigen exposure and BAL lymphocytosis (≥20%) or transbronchial biopsies demonstrating non-necrotizing granuloma(s) or lymphocytosis, or surgical lung histology consistent with HP.

    b. Compatible FHP: Evidence of lung fibrosis (as above) with any of the following:
        i. Patchy or diffuse ground-glass opacity.
        ii. Patchy, non-profuse centrilobular nodules of ground-glass attenuation
        iii. Mosaic attenuation and lobular air-trapping that do not meet criteria for typical fibrotic HP.
        AND
        iv. Lack of features suggesting an alternative diagnosis.

    These patients are required to have an identifiable or indeterminate antigen exposure and BAL lymphocytosis (≥20%) or transbronchial biopsies demonstrating non-necrotizing granuloma(s) or lymphocytosis, or surgical lung histology consistent with HP. Otherwise, surgical lung histology consistent with HP.

c. Indeterminate FHP: CT signs of fibrosis without other features suggestive of HP and lack of features suggesting an alternative diagnosis. These patients are required to have a known antigen exposure and BAL lymphocytosis (≥20%) or transbronchial biopsies demonstrating non-necrotizing granuloma(s) or lymphocytosis, or surgical lung histology consistent with HP.

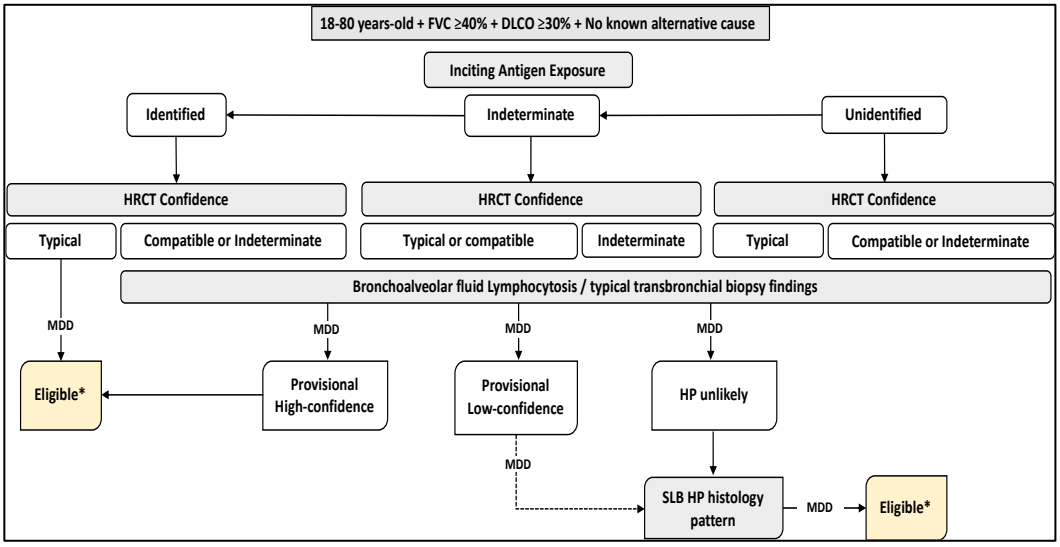
FHP Disease Severity and Progression

4. FVC ≥40%, DLCO ≥30% based either on historical pulmonary function tests obtained within the 60 days prior to Day 1
5. In the investigator's opinion, evidence of disease progression: worsening respiratory symptoms and an increased in extent of fibrosis on HRCT or relative decline in the FVC% of at least 5% over 24 months.
6. Able to walk ≥100 m during the 6-minute walk test (6MWT) at Screening.

Informed Consent and Protocol Adherence

7. Able to understand and sign a written informed consent form.
8. Able to understand the importance of adherence to study treatment and the study protocol and willing to follow all study requirements, including the concomitant medication restrictions, throughout the study

Eligibility criteria summary (multidisciplinary discussion):



***HP Diagnosis - Multidisciplinary Adjudication Committee**: the multidisciplinary discussion will be performed at the weekly NJH ILD conference attended by seven pulmonologists, one radiologist, and one pathologist. During the conference, the

exposure history (identified, indeterminate [evidence is suggestive of an association], or unidentified inciting antigen exposure), clinical details and radiologic and pathologic images will be presented. The expert chest radiologist and the expert pathologist will interpret the radiological and histological features. The final multidisciplinary diagnosis adjudication will be documented on a case report form. Differences of opinion regarding diagnostic eligibility will be resolved through consensus adjudication.
Patients with a provisional low-confidence diagnosis or HP unlikely may require surgical lung biopsy HP histology data for inclusion as determined by the adjudication committee.

EXCLUSION CRITERIA
Patients with any of the following will be excluded from the study:

Disease-Related Exclusions

1. Not a suitable candidate for enrollment or unlikely to comply with the requirements of this study, in the opinion of the investigator
2. Cigarette smoking at Screening or unwilling to avoid tobacco products throughout the study
3. Known explanation for the interstitial lung disease, including but not limited to radiation, drug toxicity, sarcoidosis, pneumoconiosis.
4. Clinical diagnosis of any connective tissue disease, including but not limited to scleroderma, polymyositis/dermatomyositis, and rheumatoid arthritis.
5. Expected to receive a lung transplant within 6 to 12 months from randomization or on a lung transplant waiting list at randomization.
6. The investigator judges that there has been sustained improvement in the severity of FHP during the 6-12 months prior to Screening Visit 1, based on changes in %FVC, %DLCO, and/or HRCT scans of the chest.

Medical Exclusions

7. Any condition other than FHP that, in the opinion of the investigator, is likely to result in the death of the patient within 6 to12 months.
8. Any condition that, in the opinion of the investigator, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone.
9. Pregnancy or lactation. Women of childbearing capacity are required to have a negative serum pregnancy test before treatment and must agree to maintain highly effective contraception by practicing abstinence or by using at least two methods of birth control from the date of consent through the end of the study. If abstinence is not practiced, one of the two methods of birth control should be an oral contraceptive (e.g., oral contraceptive and a spermicide).
10. History of ongoing alcohol or substance abuse.

11. History of severe hepatic impairment or end-stage liver disease.
12. History of end-stage renal disease requiring dialysis.
13. Clinical evidence of active infection including, but not limited to, bronchitis, pneumonia, sinusisits, or urinary tract infection.
14. Unstable or deteriorating cardiac disease, including but not limited to the following:
    a. Unstable angina pectoris or myocardial infarction.
    b. Congestive heart failure requiring hospitalization.
    c. Uncontrolled clinically significant arrhythmias.

Laboratory Exclusions

15. Any of the following liver function test criteria above specified limits: total bilirubin > 2.0 mg/dL, excluding patients with Gilbert's syndrome; aspartate or alanine aminotransferase (AST/SGOT or ALT/SGPT) >3 ULN; alkaline phosphatase >2.5 ULN within past 30 days.
16. Creatinine clearance (CrCl) <30 mL/min, calculated using the Cockcroft-Gault formula within past 30 days.
17. Electrocardiogram (ECG) with a QTc interval >500 msec at Screening.

Medication Exclusions

18. Prior use of pirfenidone, nintadinib or known hypersensitivity to any of the components of study treatment.
19. Introduction, increase or escalation of immunosuppressive pharmacological therapy within 1 month (e.g. prednisone, azathioprine, mycophenolic acid and mycophenolate mofetil).
20. Use of any of the following therapies within 28 days before Screening:
    a. Bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, methotrexate, tacrolimus, tetrathiomolybdate, TNF-α inhibitors, imatinib mesylate, Interferon gamma-1b, and tyrosine kinase inhibitors.
    b. Fluvoxamine.
    c. Sildenafil (daily use). Note: intermittent use for erectile dysfunction is allowed.

Treatments

Study treatment is defined as either pirfenidone 2403 mg/d or placebo equivalent administered in divided doses three times per day (TID) with food. Study treatment will be titrated over 4 weeks to the full maintenance dose of 9 capsules per day (three 267-mg capsules taken orally TID with food). Subjects will remain on a stable maintenance dose for the duration of the treatment period unless the dose is reduced to manage an AE or titrated again when restarting study treatment after a 28-day or greater lapse in treatment.

Missed Doses

If subjects miss a scheduled dose, that dose should be skipped. Regular dosing should

resume with the next scheduled dose. Subjects should not take any extra doses to make up for missed doses.

Study Treatment Supply
Genentech will supply all study treatment. Pirfenidone 267-mg and placebo will be supplied in opaque, hard, white gelatin capsules that are visually indistinguishable.

RANDOMIZATION AND BLINDING

This is a randomized, double-blind, placebo-controlled study. Neither study personnel nor the subjects will know which study treatment the subject is receiving. Subjects will be randomized in a 2:1 ratio to receive either pirfenidone 2403 mg/d or a placebo equivalent. The placebo will be visually similar to pirfenidone. The National Jewish Health statistician will hold the randomization schedule and the clinical research unit will keep the unidentified placebo or drug bottles for each patient prepared by Genentech. On the Day 1 visit, each subject will receive his or her first bottle of assigned unidentified drug.

Unblinding
Individual subject treatment assignments will not be unblinded during the study unless a subject safety issue arises in which unblinding is necessary to ensure optimal subject management. Once the study is complete, and the final analysis completed, treatment assignments will be unblinded for all subjects.

Study Treatment Accountability
The monitoring of the inventory of study treatment supplies will be delegated to the National Jewish Health clinical research unit. Study treatment may not be used for any purpose other than that described in the protocol. All study treatment will be stored in a secure drug storage room with access restricted to authorized personnel. Subjects will be asked to return all used and unused bottles of study treatment at every visit. All bottles of study treatment will be recorded in a Drug Accountability Log. The study coordinator at the National Jewish Health clinical research unit will account for all study treatment received, dispensed to the subjects, returned by the subjects, not used, and sent for destruction. All documentation of study treatment shipments will be retained at the National Jewish Health Clinical Research Unit.

Dispensing of Study Treatment
Study treatment will be dispensed to the subjects every 13 weeks, but may be dispensed at other visits, as needed. Subjects will be instructed to store study treatment at room temperature. Subjects will be instructed to use study treatments in the order in which they are dispensed and that they must return all used and unused study treatment bottles at every visit. Study drug returned at week 5 will be counted for compliance and returned to

the subject at those visits.

Concomitant Medications
All of the following are considered concomitant medications, and data regarding their use will be collected and recorded:
1. Prescription drugs
2. Over-the-counter drugs, including vitamins, antacids, herbal and dietary supplements
3. Permitted FHP therapies: prednisone, azathioprine, mycophenolic acid and mycophenolate mofetil
4. Excluded therapies (see exclusion criteria)

Early Discontinuation of Study Treatment
Study treatment will be discontinued for any of the following reasons:
1. Unacceptable toxicity (this may include serious adverse events [SAEs] related to
2. study treatment)
3. Patient request or withdrawal of consent
4. Pregnancy
5. Investigator discretion
6. Lung transplantation

Subjects who discontinue study treatment will be asked to complete all scheduled study assessments and procedures through Week 52.

STUDY ENDPOINTS

Primary Efficacy Outcome Variables:
Mean change in %FVC at week 52.

Key Secondary Efficacy Outcome Variables
1. Progression-free survival (PFS) defined as the time from study treatment randomization to the first occurrence of any of the following events:
    a. Relative decline from baseline in ≥10% in FVC and/or DLCO
    b. Acute exacerbation of FHP defined as acute respiratory declined leading to hospitalization or ER or Urgent care evaluation; or evidence of all of the following criteria within a 4-week period in the outpatient setting:
        i. Increase from baseline FIO2 ≥1 L O2.
        ii. Clinically significant worsening of dyspnea and/or cough.
        iii. New, superimposed ground-glass opacities or consolidation or new alveolar opacities on chest x-ray or CT.
        iv. Primary: if all other causes excluded (e.g., acute gastro-esophageal aspiration, pneumothorax, infection, left heart failure, pulmonary

embolism, or identifiable cause of acute lung injury).

c. A decrease from baseline of at least 50 meters in 6-minute walk distance.
d. Change in background therapy (need for a new course of PO or IV steroids or for the patient receiving maintenance prednisone, as a need to increase the dose by 10 mg or more; and/or addition of cyclophosphamide, azathioprine, mycophenolate mofetil or mycophenolic acid).
e. Death

2. Slope of FVC over 52-week treatment period.
3. Mean change in %DLCO at week 52
4. Proportion of patients with all-cause mortality.
5. Proportion of patients with all-cause hospitalization.
6. Proportion of patients with hospitalization for respiratory cause.
7. Proportion of patients with respiratory exacerbations requiring hospitalizations.
8. Proportion of patients with evidence of progression in fibrosis on visual comparison of baseline and week 52 HRCT scans.

Exploratory Outcome Variables:

1. Mean change from baseline in health−related quality of life, measured by St. George's Respiratory Questionnaire (SGRQ) (3 domain scores and total score), at Week 52.
2. Mean change from baseline in health−related quality of life, measured by A Tool to Assess Quality of Life Questionnaire (L-IPF) at Week 52.
3. Mean change from Baseline to Week 52 in dyspnea as measured by the University of California at San Diego Shortness-of-Breath Questionnaire (UCSD SOBQ) score.
4. Proportion of patients with evidence of progression, stability or improvement in fibrosis on texture-based quantitative analysis of CT.
5. Candidate biomarker expression in the peripheral blood of patients with HP over the 52-study follow-up period.

Safety Outcome Measures:

1. Proportion of patients with treatment-emergent adverse events (AEs)
2. Proportion of patients with treatment-emergent serious adverse events (SAEs)
3. Proportion of patients with treatment-emergent adverse drug reaction (ADRs)
4. Proportion of patients with treatment-emergent serious drug reaction (SDRs)
5. Proportion of patients with AEs leading to early discontinuation of study treatment
6. Proportion of patients with treatment-emergent deaths
7. Proportion of patients with treatment-emergent changes in clinical laboratory findings, vital signs and ECGs.

STUDY ASSESSMENTS

Patients will be screened for study inclusion over a period of up to 4 weeks. If eligible, subjects will receive study drug starting on Day 1 (clinic visit). Subjects will have a telephone assessment at Week 1 and 3 and in-clinic assessments on week 5, 13, 26, 39, and 52. Study assessments will include laboratory tests, spirometry, DLCO, 6MWT and Borg Scale, ECG, HRCT scan, patient reported outcome questionnaires, vital signs, height, weight, oxygen saturation and fraction of inspired oxygen (FiO2), directed history, physical examination and any changes to existing treatment regimens. Subjects will complete an AE and dosing compliance diary between all visits. Subjects who undergo lung transplantation or who chose to withdraw from study procedures early will be followed for vital status until Week 52.

Routine Clinical Laboratory Tests

The following assessments will be performed at the National Jewish Health Advanced Diagnostic Laboratories:

1. Hematology (complete blood count with platelet count and automated differential)
2. Serum chemistry profile
3. Pregnancy test for women of childbearing capacity

Biomarkers in blood

The study will include a significant exploratory component focused on identification of biomarkers that may be prognostic for patients likely to have an accelerated rate of disease progression or diagnostic for identifying patients likely to benefit from treatment. Certain biomarkers may be differentially expressed in FHP and may change as a result of pirfenidone treatment. The blood samples that will be obtained for this study may help identify these biomarkers. Serum and plasma samples will be collected at baseline and at week 52 to assess the relationship between FHP related biomarkers (identified by RNA-seq and ChIP-seq), disease progression, clinical status, and treatment benefit. We hypothesize that distinct peripheral blood mononuclear cells gene expression profiles have the potential to be an adjunct to the traditional clinical-radiologic-pathologic assessment, in providing disease-specific prognostic information and help identify novel pathways for targeted therapy.

HRCT Scans

HRCT scans obtained within 4 months before the Screening period as part of the standard of care for a patient may be used to confirm eligibility, provided they meet all of the image acquisition and quality criteria required by the CT expert readers. All HRCT digital images are to be stored on a dedicated disk. The images will be anonymized using a tool developed by the Quantitative Imaging Laboratory at National Jewish Health. The Quantitative Imaging Laboratory will be tasked with interpretation, archiving, and quantitative analysis of the images. One thoracic radiologist with expertise in FHP will review the HRCT scans using an electronic score sheet. Data regarding the HRCT interpretation will be entered electronically

into the trial research's database and incorporated into the clinical database. Evidence of progression, stability, or improvement in fibrosis on temporally blinded visual comparison of baseline and week 52 HRCT scans will be documented on a five-point scale (much better, better, same, worse, and much worse).

Pathology

For patients with surgical lung biopsies or bronchoscopic biopsies, a score sheet will be used to assess whether or not the biopsy is consistent with a diagnosis of hypersensitivity pneumonia and to record the associated histologic findings. One thoracic pathologists will score each biopsy. If a patient will be excluded from the study based on the pathology assessment by a single reader, a second reader will be used to resolve the discrepancy. The microscopic features section of the score sheet will be recorded for each read and since they represent semi-quantitative data, the mean will be used as the overall result for later analysis. The microscopic section of the score sheet will not be used to determine subject inclusion/exclusion.

Score sheet:
Biopsy type: Bronchoscopic, Wedge
<u>Diagnosis:</u>
Is the biopsy consistent with a pathologic diagnosis of hypersensitivity pneumonia:
If the biopsy is inconsistent, what is your overall diagnosis?
<u>Microscopic findings:</u>
Please assess the extent of each of the following on a scale 0-3 (0 = none, 1 = mild/rare, 2 = moderate, 3 = severe/extensive)
Airway-centered chronic inflammation:
Nonnecrotizing granulomas:
Multinucleated giant cells:
Peribronchiolar metaplasia:
Organizing pneumonia:
Fibrosis:
Microscopic honeycombing:

Spirometry and DLCO Measurements

All equipment, procedures, and personnel qualifications for the assessment of lung function are based on the recommendations of the American Thoracic Society:

1. Spirometry measurements will include FVC and FEV1
2. DLCO will be measured by determining the diffusing/transfer capacity of the lung for carbon monoxide.

Data for FVC, DLCO will be entered electronically blindly into the research's database and incorporated into the research electronic data capture (REDCap).

6-Minute Walk Test (6MWT) and Borg Scale
The 6MWT measures the distance that a patient can walk at his/her own pace on a measured, flat hard surface in a period of 6 min. The 6MWT assesses the global and integrated responses of all body systems involved during walking. The 6MWT will be performed based on ERS/ATS recommendations. The Borg Scale is an instrument to be self-administered by the patient as part of the 6MWT procedure.

St George's Respiratory Questionnaire (SGRQ)
The SGRQ is patient-self-administered questionnaire to measure and quantify health-related health status. It has been shown to correlate well with established measures of symptom level, disease activity and disability.

A Tool to Assess Quality of life in (L-IPF)
The L-IPF is patient-self-administered questionnaire to measure and quantify health-related health status developed at National Jewish Health.

UCSD Shortness of Breath Questionnaire
The UCSD SOBQ is a symptom-specific, 24-item, patient-self-administered questionnaire that will be use to assess shortness of breath on the study subjects while doing a variety of activities of daily living.

Physical Exam and Vital Signs
A complete physical examination will be performed by a study physician and will include all body systems pertinent to the subject. If clinically significant abnormalities are observed before Day 1, they will be reported in the patient's medical history. If clinically significant abnormalities are observed after Day 1, the investigator will decide if they are new adverse events. Vital signs for this study protocol include heart rate, blood pressure, oxygen saturation and FiO2.

Electrocardiograms (ECGs)
During the study, if the QTc interval is >550 msec. and verified by the study site or local cardiologist, study drug will be stopped. If the QTc interval is between 500 and 550 msec. and verified by a study site study treatment will be interrupted. ECG data will be incorporated into the clinical database.

Directed History During the Study
The following will be assessed as directed history:
- Clinical and exposure history.
- AEs/SAEs.
- Concomitant medications.

- Dosing and compliance.
- Supplemental oxygen use.
- Hospitalizations.

Vital Status Assessments

Vital status will be assessed for those who are no longer able to participate in the study procedures (Early Withdrawal from Study Procedures) at protocol-specified time points (study visit dates) until the Follow-Up Visit. Subjects who undergo lung transplantation or who chose to withdraw from study procedures early will be followed for vital status until Week 52. This assessment will most likely be accomplished remotely (i.e., via telephone or electronically). These communications are well documented in the participants study file. Vital status procedures are as follows:

1. If the subject is not available, an authorized family member or representative will be contacted by telephone or electronically at the milestones of study visit dates.
2. In the case of lung transplant, the date of the transplant, details of the transplant, dates of hospitalization, and the current vital status will be obtained.
3. In the case of a subject death, the date, details, and cause of death will be requested from the subject's representative or family member.
4. If a subject is lost to follow-up, vital status will be ascertained through the use of death registries.

Mortality Assessment

Mortality Assessment will be closely examined by Tristan Huie, MD including the details and the relationship to FHP for each death. Documentation regarding deaths must be requested and should include (but is not limited to) discharge summaries, death certificates, and autopsy reports.

Washout and Screening Periods

Written informed consent will be obtained before initiating any study-associated procedures or changes to a pre-existing treatment regimen for purposes of this study. Procedures conducted during Screening will be used to determine the eligibility of each patient for study inclusion before randomization and to establish subject Baseline status. If subjects fail Screening due to a condition that subsequently resolves (e.g., infection), they may be considered for rescreening.

Washout Period (28 Days)

Before entering a subject in the Washout Period, all relevant medical history, diagnostic findings, and measures of disease severity should be reviewed to evaluate the subject's suitability for the study. Written informed consent must be obtained before withdrawing or tapering the subject off prohibited therapies. The study team must explain to the subject that entry into the study is not guaranteed. Any subject identified for the study must

discontinue all prohibited medications at least 28 days before Screening. This is the Washout Period. If a medication must be tapered, tapering must start early enough that the subject has discontinued the drug 28 days before the start of Screening.

Screening Period

The Screening period is defined as the time between the date of the first Screening procedure and may last up to 30 days. Screening procedures may be conducted on different days within the Screening period if convenient.

The following procedures will be performed during Screening:

1. Written informed consent, if not already obtained during the Washout Period.
2. Complete medical history, review of systems, and review of concomitant medications.
3. Physical examination, vital signs, weight, and height.
4. Clinical laboratory assessments, including hematology, serum chemistries, serologic tests clinically within the past 30 days, and pregnancy test for women of childbearing capacity.
5. ECG.
6. Resting Oxygen and FIO2.
7. A 6MWT with Borg Scale pre and post.
8. Transfer of all surgical lung biopsies, if available, for evaluation by pathologist.
9. Review of transbronchial biopsy and/or BAL, if available, to assess eligibility
10. HRCT within the past 4 months, spirometry and DLCO within the past 30 days to assess eligibility.

Assessments during Treatment

Eligibility and Randomization (Day 1)

All Day 1 procedures must be performed before randomization and before administration of study treatment. This study has no Day 0. Randomization (Day 1) will occur no more than 30 days after the start of the Screening period, and study treatment will begin on the day of randomization. Once the patient is confirmed to be eligible for randomization, the patient will be randomized at the end of Day 1.

The following procedures will be performed on Day 1:

Before Randomization

1. Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, and hospitalizations).
2. Physical examination, vital signs, FiO2 and weight.
3. Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity.
4. Spirometry (FVC, FEV1) and DLCO.
5. 6MWT with Borg Scale pre and post.

6. UCSD SOBQ, L-IPF and SGRQ.
7. Confirmation of patient eligibility for study participation.
8. Genetic testing (RNA-seq and ChIP-seq).

Randomization

9. All unidentifiable randomization codes will be generated by a statistician independent of the trial conduct. All subjects, monitors, and study center personnel related to the study, including the site pharmacist will be blinded to study treatment throughout the study. The randomization schema will be securely maintained electronically at the NJH Clinical Research Unit.

After Randomization

10. Instruct the subject on how to titrate the dose of study treatment.
11. Dispense 13-week supply of study treatment. Dosing should start on the day of randomization (see clinical IB section 3).
12. Dispense subject diary and instruct on its use.

Week 1 Telephone Assessment (± 2 days)

A telephone interview will be conducted to determine vital status and to assess tolerability of study treatment, subject compliance with dosing, and titration of study treatment.

Week 3 (± 2 days)

The following will be performed at Week 3:
1. On-site safety assessment.
2. Clinical laboratory assessments including comprehensive metabolic panel.

Week 5 (± 1 week)

The following procedures will be performed at Week 5:
1. Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary).
2. Physical examination, vital signs, FiO2 and weight.
3. ECG.
4. Clinical laboratory assessments, including hematology, serum chemistries, and pregnancy test for women of childbearing capacity.
5. Vital Status Assessment.

Week 13 (± 2 weeks)

The following will be performed at Week 13:
1. Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary).
2. Physical examination, vital signs, FiO2 and weight.

3. ECG.
4. Spirometry (FVC, FEV1).
5. Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity.
6. 6MWT with Borg Scale pre and post.
7. UCSD SOBQ, L-IPF and SGRQ.
8. Collection of any unused study treatment, review compliance and dispensing of 13-week supply of study treatment.
9. Dispense new diary, if required.
10. Vital Status Assessment.

Week 26 (± 2 weeks)
The following will be performed at Week 26:
1. Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary).
2. Physical examination, vital signs, FiO2 and weight
3. ECG.
4. Spirometry (FVC, FEV1)/DLCO.
5. Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity.
6. 6MWT with Borg Scale pre and post.
7. UCSD SOBQ, L-IPF and SGRQ.
8. Collection of any unused study treatment, review compliance and dispensing of 13-week supply of study treatment.
9. Dispense new diary, if required.
10. Vital Status Assessment.

Week 39 (± 2 weeks)
The following will be performed at Week 39:
1. Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary).
2. Physical examination, vital signs, FiO2 and weight
3. ECG.
4. Spirometry (FVC, FEV1).
5. Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity.
6. 6MWT with Borg Scale pre and post.
7. UCSD SOBQ, L-IPF and SGRQ.
8. Collection of any unused study treatment, review compliance and dispensing of 13-week supply of study treatment.
9. Dispense new diary, if required.

10. Vital Status Assessment.

Week 52 (± 1 week)
Study treatment will stop for all subjects upon completion of all procedures for the Week 52 Visit. Subjects must return all used and unused study treatment bottles from this study to the study center. The following procedures will be performed at the Week 52 Visit:
1. Directed medical history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary).
2. Physical examination, vital signs, FiO2 and weight.
3. ECG.
4. Clinical laboratory assessments, including hematology, serum chemistries, and pregnancy test for women of childbearing capacity, and genetic testing.
5. Spirometry (FVC, FEV1)/DLCO.
6. 6MWT and Borg Scale pre and post.
7. UCSD SOBQ, L-IPF and SGRQ.
8. HRCT.
9. Collection of all used and unused bottles of study treatment.
10. Dispensing of a new diary, if required, for data collection during Follow Up.
11. Vital Status Assessment.
12. Genetic testing (RNA-seq and ChIP-seq).

Follow-up Visit (+ 7 days)
Patients who discontinue study treatment early will be required to return for a Follow-up Visit 28 to 35 days after their last dose of study treatment in this study. The following procedures will be performed at the Follow-up Visit:

1. Directed medical history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary).
2. Physical examination, vital signs, and weight.
3. Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity.
4. Collection of diary.
5. Vital Status Assessment.

Early Discontinuation of Study Treatment
Subjects who discontinue study treatment before Week 52 will complete a Follow-up Visit. In addition to the procedures listed above for the Follow-up Visit, subjects who discontinue study treatment before Week 52 must return all used and unused study treatment. Subjects who discontinue study treatment will be asked to continue to complete all scheduled study assessments and procedures through Week 52.

Early Withdrawal from Study Procedures
Subjects who withdraw from study procedures early for reasons other than withdrawal of consent will cease study procedures but should be reminded that they gave permission for Vital Status Assessments when they consented to participate in the study. Consent for Vital Status Assessments remains intact when a subject withdraws from study procedures. Such subjects will continue to complete Vital Status Assessments through Week 52. Subjects who withdraw consent in writing will cease all study procedures including vital status assessments.

Study Treatment Pre-Restart and Restart Visits
Subjects should be encouraged to restart study treatment whenever possible and appropriate. If the subject has interrupted study treatment for ≥28 days, Restart Visits are required. The Pre-Restart Visit will be conducted on the day study treatment is resumed, followed by Restart Visits at Weeks 1, 3 (phone visits); 5, and 13 to be scheduled based on the date of study treatment restart. The following procedures will be performed at the Pre-Restart Visit:

1. Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, and hospitalizations, clinical and exposure history).
2. Physical examination, vital signs, and weight.
3. Clinical laboratory assessments, including hematology, serum chemistries, and pregnancy test for women of childbearing capacity.
4. Instruction on how to re-titrate the dose of study treatment.
5. Dispensing of study treatment, as necessary.
6. Dispensing of patient diary, as necessary.

Visit requirements and visit windows for Restart Week 1 and 3 (phone visits) and Restart Weeks 5, and 13 are the same as those described above.

Subjects who restart study treatment will resume the visit schedule based on their date of randomization. If a regularly scheduled visit (Weeks 13, 26, 39, etc.) coincides with one of the Restart Visits (Restart Weeks 5), then all of the elements of the regularly scheduled visit should be performed in lieu of the Restart Visit (see clinical IB section 3).

QTc Monitoring
During the study, if the QTc interval is >550 msec., confirmed by a repeat ECG within 24 h, the study drug will be interrupted until the reading is confirmed by the ECG safety officer. If the reading is confirmed, the subject will be discontinued from study treatment. If the QTc interval is between 500 and 550 msec., confirmed by a repeat ECG within 24 hours, study treatment will be interrupted. If an alternative explanation is identified (e.g., electrolyte abnormality or concomitant medication), re-initiation of study treatment will be considered

by the investigator. ECG data will be entered directly into the research's database.

Patients Lost to Follow-Up

If a subject has missed a visit and is not responding to no more than 2 attempted telephone calls from the site (all attempts to contact the subject should be documented). The site should then make no more than 2 attempts to contact the subject's emergency contact. If these attempts are not successful, a registered letter should be sent to the last known address of the subject. If this is not successful, as a last resort, the site should check the national death registries, where approved by regulatory authorities and available. If this is unsuccessful, the subject will be considered lost to follow-up.

STATISTICAL METHODS

Randomization and Treatment Assignment

In this double-blind study, subjects will be randomized to receive either pirfenidone 2403 mg/d or placebo in a 2:1 ratio.

Sample Size and Power Considerations

The sample size and power calculations for this study are based on the primary endpoint, mean change in %FVC from Baseline to Week 52. Estimates are based on the results from the National Jewish Health pilot data of FHP (N=30 patients with biopsy and HRCT FHP pattern). For the primary efficacy comparison of change in mean %FVC between the treatment (2403 mg/d) and placebo groups, about 13 patients in the placebo and 25 (N=38) in the treatment group will provide at least 85% power to detect a mean difference between groups of 2%. Assuming a 10% attrition rate approximately 42 subjects will be enrolled and randomized in a 2:1 ratio to pirfenidone 2403 mg/d or placebo.

These calculations assume a standard deviation in the %FVC change from baseline to 52 weeks of 2% and are based on a 2-sample means t-test with a 2-sided Type I error probability of 0.05.

Analysis Populations

The intent-to-treat population, consisting of all subjects who signed the informed consent form and were randomized, will be used as the primary population for efficacy analyses. The safety analysis population will include all subjects who signed informed consent and received any amount of study drug. The trial results will be reported according to guidelines specified in the Revised Consolidated Standards of Reporting Trials (CONSORT) statement.[23] A flow diagram describing screening, recruitment, randomization, dropout, and vital status will be included in the primary study report.

Statistical Analyses

Demographic and Baseline Data
Descriptive statistics will be used to summarize demographic, baseline subject characteristics and to assess safety. Continuous-scaled variables (e.g., age) will be summarized with means, medians, standard deviations, quartiles, and minimum and maximum values. Categorical variables (e.g., sex) will be summarized using patient counts and percentages.
Baseline medical histories, medications and pre-existing conditions will be summarized by treatment groups.

Efficacy Analyses

Primary Efficacy Outcome Variable and Analysis
The primary efficacy analysis will estimate the mean rank change in %FVC from Baseline to Week 52. Data will be analyzed using a rank linear regression model with the rank change in %FVC from Baseline to Week 52 as the outcome variable and rank Baseline %FVC and HP therapy (placebo or pirfenidone) and concomitant immunosuppressive therapy as covariates. The treatment effect will be tested using the Wald test.
The primary efficacy analysis will be tested at an alpha level of 0.05. Missing data due to reasons other than death will be replaced with imputed values using the MICE method (multiple imputation via chained equations).[24] Missing data due to lung transplant will be imputed using the MICE method even if the subject dies after lung transplant.
Subjects with missing assessments due to death will be ranked worse than those who remain alive. Subjects who die will be ranked according to the time until death, with the shortest time until death as the worst rank.
Supportive analyses of the primary efficacy outcome will include the following:
1. Landmark analyses of mean change in %FVC from Baseline to Weeks 13, 26, 39 and 52.
2. Mean rank change in %FVC compared to Baseline across all study time points using a rank linear mixed effects model for repeated measures.

Key Secondary Efficacy Outcome Variables and Analyses
Multiplicity adjustment will be performed across all secondary endpoints.

Progression-free survival will be compared between the pirfenidone 2403 mg/d and placebo groups using the log-rank test. A proportional hazards model will be used to estimate the hazard ratio. Descriptive analysis of progression free survival will be presented using Kaplan-Meier curves. Mortality will be analyzed using logistic regression with a treatment effect and accounting for potential over- or under-dispersion in the outcome.

The slope for annual rate of FVC decline will be analyzed using a random coefficient regression model with treatment and baseline FVC as covariates.

DLCO will be analyzed using a rank linear regression model with the rank change in %DLCO

from Baseline to Week 52 as the outcome variable and rank Baseline %DLCO and HP therapy as covariates.

Non-elective hospitalization from any cause and CT progression of fibrosis will be compared between the pirfenidone 2403 mg/d and placebo groups using logistic regression accounting for possible over- or under-dispersion in the outcome.

Exploratory Outcome Variables

Questionnaire-based outcomes comparing Baseline to 52 weeks will be analyzed using a linear regression model with a separate intercept for each subject, a dichotomous time-point effect, and a multiplicative interaction between time-point and treatment.

Changes in texture-based quantitative analysis of CT progression of fibrosis will be analyzed using multinomial regression with a separate intercept for each subject, a dichotomous time-point effect, and a multiplicative interaction between time-point and treatment.

Statistical analyses of RNA-seq and ChIP-seq results from PBMC samples will be performed with the DESeq2 packagein the R language. The p-values of Wald tests for differential expression will be adjusted using the Benjamini-Hochberg false discovery rate procedure to account for multiple testing after filtering out genes with mean normalized counts below a threshold. Significantly differentially expressed genes will be assigned to biochemical pathways and functional categories using KEGG and Gene Ontology databases using tools including GATHER, DAVID, R packages such as KEGGprofile and topGO, as well as Ingenuity pathway analysis. Diversity of immune cell types will be derived from the gene expression profiles of each sample to ensure valid comparisons and modeling. Expression profiles (baseline and week 52) will be correlated within the two HP arms using an ANOVA analysis.

Safety Analyses

Adverse event and drug reaction outcomes will be presented using standard summary statistics.

AEs will be mapped to system organ classes and preferred terms in MedDRA. Treatment emergent events are defined as those that start or worsen after the start of study treatment and up to 28 days after the last dose of study treatment. AEs will be summarized by treatment group, system organ class, and preferred term, and also by event severity and by the event's relationship to study treatment. At each level of summation, subjects will be counted only once, under the greatest severity and strongest study-drug relationship (as reported by the investigator).

Clinical laboratory data will be summarized for each treatment group at each measurement time point and for each subjects final post-Baseline measurement in the following ways: (1) with descriptive statistics (mean, standard deviation, median, and range) for each

measurement time point; (2) with descriptive statistics for the change from Baseline in the measurements at each post-Baseline time point; and (3) with shift tables summarizing the frequencies of patients below, within, and above the normal ranges at each time point as compared with Baseline. All clinical laboratory values collected during the study will be listed, with values outside the normal ranges flagged for clinical evaluation. Grade 3 and 4 laboratory results will be listed and summarized. Vital signs will be summarized by treatment group and listed for each patient. Concomitant medications will be summarized by treatment group based on mapping to drug classes and generic terms in the WHO Drug Dictionary.

Trial Monitoring

Throughout the study, the safety officer will review individual SAE reports and laboratory toxicities. In addition, the safety officer will review all safety data after 50% of enrollment is completed as well as SAEs on an ongoing basis. At all times during the course of the study, the safety officer may request access to unblinded data if needed.

SAFETY REPORTING OF ADVSERSE EVENTS

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:

1. AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with FHP that were not present prior to the AE reporting period.
2. Complications that occur as a result of protocol-mandated interventions (e.g. procedures such as 6 Minute Walk Test).
3. If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
4. 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:

1. It results in death (i.e., the AE actually causes or leads to death).
2. 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.).
3. It requires or prolongs inpatient hospitalization.
4. 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).
5. It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
6. 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).

Methods and Timing for Assessing and Recording Safety variables

The study team 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).

Adverse Event Reporting Period

The study period during which all AEs and SAEs as described in *section J* where the patient has been exposed to Genentech product must be reported begins after informed consent is obtained and the 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.

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 (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 the study drug (Pirfenidone); 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 (Pirfenidone) (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.

Procedures for Eliciting, Recording, and Reporting Adverse Events

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?"

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:

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

e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) Update current versions) 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
Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
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.
If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
Grade 4 and 5 events must be reported as serious adverse events

f. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 90 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 90 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.

g. 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. Including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period

h. Reconciliation

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via sponsor emailing Genentech a Quarterly line-listing documenting single case reports sent by sponsor to Genentech in the preceding time period.
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 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)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

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:
   a. Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
   b. Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice
2. Suspected transmission of an infectious agent by the study drug, as defined below:
   a. 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

The *Pirfenidone* Events of Special Interest are: None

i. Exchange of SINGLE CASE REPORTS

Sponsor will track all protocol-defined AE Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports and pregnancy reports originating from the Study for the Product and and Product Complaints (with or without an AE) originating

from the Study for the Product.

Investigators must report all Adverse Events/ Serious Adverse events (SAEs), AEs of Special Interest (AESIs) pregnancy reports and special situation reports (if applicable) adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed immediately upon completion to Genentech Drug Safety at:

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

All Product Complaints *without* an AE should be sent to:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.
These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

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

AESIs
AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

Special Situation Reports
Pregnancy reports
While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), 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.

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.

Non-serious ADRs
Non-serious ADRs shall be transmitted to Genentech 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).

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

1. Data related to the Product usage during pregnancy or breastfeeding
2. Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
3. Lack of therapeutic efficacy
4. Drug interaction
5. Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be 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)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported

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.

MedWatch 3500A Reporting Guidelines

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

1. Protocol description (and number, if assigned)
2. Description of event, severity, treatment, and outcome if known
3. Supportive laboratory results and diagnostics
4. 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:

1. Adding to the original MedWatch 3500A report and submitting it as follow-up
2. Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
3. 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 and 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

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where

it has filed a clinical trial approval, in compliance with local regulations

Genentech 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.

National Jewish Health 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.

National Jewish Health will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Additional Reporting Requirements for IND Holders (if applicable)

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

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/Roche within 7 calendar days of first learning of the event.

Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of Pirfenidone. An unexpected adverse event is one that is not already described in the Pirfenidone investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning

similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech/Roche, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to
Genentech/Roche Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

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 sent to the assigned Clinical Operations contact for the study:

Esbriet Clinical Operations:
Email: esbriet-gsur@gene.com
Fax: (866) 312-5695

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

Sponsor will forward a copy of the Publication to Genentech/Roche upon completion of 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 sponsor. 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. National Jewish Health 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. National Jewish Health 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.

Randomization Codes for blinded clinical trials (if applicable)

The blind will be broken for ADR reports that are Serious and Unexpected, unless otherwise agreed with applicable regulatory authorities.

IND Annual Reports

Copies to Genentech:

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 238-6067

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

Initial Report Date	[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]
Follow-up Report Date	[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]
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

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