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Early View

Study protocol

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Design and Rationale of Randomized, Double-Blind Trial of the Efficacy and Safety of Pirfenidone in Patients with Fibrotic Hypersensitivity Pneumonitis

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Message: We describe the design of a Phase II study of 52 weeks' pirfenidone or placebo on top of standard of care, in patients with fibrotic HP (ClinicalTrials.gov: NCT02958917)

Plain language summary: Every day, our lungs are exposed to outside substances, such as mold, bacteria, bird droppings and more. In some people, inhaling these foreign substances can lead to inflammation and a condition called hypersensitivity pneumonitis (HP). The inflammation is caused by an immune reaction to these foreign substances. HP comprises several hundred conditions that reside within the broad category of interstitial lung diseases (ILD) and are characterized by scarring and/or inflammation of the interstitium – the area surrounding the air sacs at the end of each airway in the lungs. People can develop a chronic form of HP, which can lead to permanent scarring (fibrosis, fibrotic HP – FHP) in the lungs that gets worse over time. FHP is not reversible, and patients who develop fibrosis have a higher risk of death than patients with HP who do not develop fibrosis. A prescription medicine called pirfenidone is used to treat certain forms of pulmonary fibrosis, and we hypothesized that it could treat FHP. This report describes the study design of a clinical trial looking at pirfenidone treatment in adults with FHP (ClinicalTrials.gov: NCT02958917).

ABSTRACT

Hypersensitivity pneumonitis (HP) is an immunologically mediated form of lung disease resulting from inhalational exposure to any of a large variety of antigens. A subgroup of patients with HP develops pulmonary fibrosis (fibrotic HP, FHP), a significant cause of morbidity and mortality. This study will evaluate the safety and efficacy of the antifibrotic pirfenidone in treating FHP.

This single-center, randomized, double-blind, placebo-controlled trial is enrolling adults with FHP (ClinicalTrials.gov: NCT02958917). Study participants must have fibrotic abnormalities involving ≥5% of the lung parenchyma on high-resolution CT scan, forced vital capacity ≥40% and diffusing capacity of the lung for carbon monoxide ≥30% of predicted values. Study participants will be randomized in a 2:1 ratio to receive pirfenidone 2403 mg/d or placebo. The primary efficacy endpoint is the mean change in %FVC from baseline to week 52. A number of secondary endpoints have been chosen to evaluate the safety and efficacy in different domains.

INTRODUCTION

Background and rationale

Hypersensitivity pneumonitis (HP) is an immunologically mediated form of lung disease, resulting from inhalational exposure to a large variety of antigens. In the United States, the estimated yearly prevalence of HP ranges from 1.67 to 2.71 cases per 100,000 persons. Between 56% and 68% of HP cases in per year are considered chronic disease (prevalence, 0.9–1.7 per 100,000 persons) and among chronic cases approximately 36 to 48% have pulmonary fibrosis.[1] A large proportion of patients with fibrotic HP develop symptomatic, functional and radiographic disease progression.[2-4] Progressive fibrotic HP (FHP) has a mortality rate

comparable to idiopathic pulmonary fibrosis (IPF) with an estimated mean survival of 3 to 5 years from the time of diagnosis.[2,5,6]

Pirfenidone is an antifibrotic agent that downregulate collagen synthesis, decreases the extracellular matrix, and blocks fibroblast proliferation in vitro.[7] Results from previous clinical trials have shown that pirfenidone is safe and well tolerated and significantly slow the rate of disease progression, as measured by a declining FVC in patients with IPF.[8-11] As IPF is a fibrosing ILD that shares clinical and pathobiological features with FHP, the use of this drug in progressive FHP has a mechanistic rationale and may be beneficial.[12-15]

This report describes the design of a phase 2 randomized, double-blind, placebo-controlled trial looking at safety, tolerability and efficacy of pirfenidone in adults with FHP.

MATERIAL AND METHODS

Study design

This is a double-blind, randomized, placebo-controlled trial (Clinicaltrials.gov: NCT02958917) being conducted at National Jewish Health (NJH), Denver, CO. Patient enrollment began in May 2017. Approximately 40-42 subjects meeting eligibility criteria for the study will be randomized in a 2:1 ratio to receive pirfenidone 2403 mg/d or placebo for 52 weeks (**Figure 1**). The dose of study drug will be titrated over 4 weeks: 2 weeks at a starting dose of 1 capsule (267 mg oral capsule with food) 3x daily; then 2 weeks at 2 capsules 3x daily; and 48 weeks at a maintenance dose of 2403 mg/day (3 capsules 3x daily).

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.

Study population

Eligible patients aged 18–80 years with HP or with a provisional high-confidence diagnosis will be identified by integration of the clinical, imaging, bronchoscopic and, when available, surgical lung biopsy data during the multidisciplinary discussion performed at the weekly NJH ILD conference (Table 1). The final consensus multidisciplinary diagnosis adjudication will be documented on a case report form.

High-resolution computed tomography (HRCT) scans must have the presence of fibrotic abnormalities affecting ≥5% of the lung parenchyma (as determined by the trial chest radiologist), with or without traction bronchiectasis or honeycombing.

There must be no evidence of an alternate diagnosis. Patients will be required to have a pre-bronchodilator forced vital capacity (FVC) ≥40% and diffusing capacity of the lung for carbon monoxide ≥30% of predicted values at screening. The screening period may last up to 30 days. Study participants must also have progressive disease defined as worsening respiratory symptoms and either an increased in extent of fibrosis on high-resolution CT or relative decline in the FVC% of at least 5% in the 24 months before screening, despite management deemed appropriate in clinical practice. Other inclusion and exclusion criteria for this study are listed in **Table 1**.

Study drug administration and blinding

Neither study personnel nor the subjects will know which study treatment the subject is receiving. Subjects will be randomized by a computer-generated randomization schedule in a 2:1

ratio to receive either pirfenidone 2403 mg/d or a placebo equivalent on top of standard of care, including antigen avoidance and abatement procedures.

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.

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.

Concomitant medications

All of the following are considered concomitant medications, and data regarding their use will be collected and recorded: prescription drugs, over-the-counter drugs, including vitamins, antacids, herbal and dietary supplements. Study participants who are receiving a stable dose of azathioprine (AZA) or mycophenolate mofetil (MMF) for >1 month before screening and who are expected to remain on a stable dose are eligible for inclusion in the trial. For excluded therapies see exclusion criteria (**Table**).

Discontinuation of study treatment

Study treatment will be discontinued for any of the following reasons: Unacceptable toxicity (this may include serious AEs related to study treatment), patient request or withdrawal of consent, pregnancy, investigator discretion or lung transplantation. Subjects who discontinue

study treatment will be asked to complete all scheduled study assessments and procedures through week 52. If new therapies are approved over the course of the trial, participants will be notified and re-consented both verbally and in writing.

Safety monitoring and ethics

Throughout the study, the safety officer will review individual serious AE reports and laboratory toxicities. In addition, the safety officer will review all safety data after 50% of enrollment is completed as well as serious AEs on an ongoing basis. At all times during the course of the study, the safety officer may request access to unblinded data if needed. Additional ad hoc meetings can be requested at any time by the safety officer or sponsor if necessary.

This trial is being conducted following the International Conference on Harmonisation guideline for Good Clinical Practice and in compliance with the ethical principles of the Declaration of Helsinki and the sponsor standard operating procedures. All documents are initially approved by the NJH institutional review board (HS-3034). Written informed consent will be obtained from all participants before trial participation.

Study endpoints

The primary endpoint of the study is the mean change from baseline to week 52 in %FVC. There are a number of secondary endpoints listed in **Table 2**. Exploratory outcomes include quantitative HRCT scores, biomarker expression and patient reported outcomes including the University of California at San Diego Shortness-of-Breath questionnaire, St. George's Respiratory questionnaire, and the Living with IPF questionnaire.

Sample size and statistical analysis

This study's sample size and power calculations are based on the primary endpoint, mean

change in %FVC from Baseline to week 52. Estimates were derived from the results of a 52-week NJH pilot study of 30 FHP patients with disease progression defined by lung function decline, independent of prior treatment received. Based on the results of that study, calculations assumed 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. For the primary efficacy comparison of the change in mean %FVC between the treatment and placebo groups, 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 at least 2%. Assuming a 10% attrition rate, approximately 42 subjects will be enrolled and randomized in a 2:1 ratio to pirfenidone or placebo.

Primary analyses

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 multiple imputation via chained equations method.[16]

Secondary endpoints analyses

Multiplicity adjustment will be performed across all secondary endpoints. Progression-free survival will be compared between the pirfenidone 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.

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 and placebo groups using logistic regression. Adverse event and drug reaction outcomes will be presented using standard summary statistics.

Analysis of study population

The intent-to-treat population, consisting of all subjects who signed the informed consent form and are 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. A flow diagram describing screening, recruitment, randomization, dropout, and vital status will be included in the primary study report.

DISCUSSION

This is the first randomized placebo-controlled trial of pirfenidone for patients with FHP. Results will provide preliminary information on the safety and dose-exposure of pirfenidone and its effect on several primary, secondary, and exploratory endpoints in FHP subjects.

A phase III clinical trial has recently investigated the anti-fibrotic nintedanib's efficacy and safety in patients with different forms of progressive fibrosing ILD, including FHP.[17] Compared with placebo, nintedanib significantly reduced the annual rate of decline in FVC (ml/year) in these patients. However, post-hoc analyses of the effect of nintedanib versus placebo on reducing the annual rate of FVC decline among subjects with FHP was not substantially different (difference 73.1, 95% CI –8.6 to 154.8). As of now there are no randomized controlled trials of pirfenidone in FHP.

The trial design considered several important methodological factors: First, we aimed to ensure the inclusion of a well-phenotyped patient population in whom there was high confidence in the diagnosis of FHP. Because no single test can confidently establish or exclude a diagnosis of HP, and diagnostic variability is common, we elected to enroll only subjects whose diagnosis of FHP came via consensus of a multidisciplinary team discussion. Doing so decreases the likelihood of misclassification. Second, inclusion criteria enrich for patients who are most likely to progress over a 52-week trial. Third, at the start of the trial in 2018, a 2:1 randomization was chosen to hasten recruitment, increase the odds of patients receiving active treatment (given the high unmet medical need), and increase the power to gather safety data, particularly on subjects on background immunosuppressive therapy. Lastly, limited data are available in the medical literature about concomitant medication use among FHP patients. Concomitant FHP treatment with oral AZA (≤ 2mg/kg daily) or MMF (≤ 1.5g twice daily) is permitted if patients

had received a stable dose for ≥ 1 month prior to enrollment. Such immunomodulatory therapies are commonly used to treat FHP, so excluding patients on background therapy would limit enrollment and our ability to generalize results to the real-world. The primary endpoint will be analyzed using a linear regression model with concomitant immunosuppressive therapy as a covariate to minimize the risk of bias. Since MMF and AZA are commonly used in FHP, and it is important that any new FHP therapy can be tolerated in conjunction with these medications, we elected to use a longer pirfenidone titration (over 4 weeks, instead of 2) to optimize tolerability.[18]

The rationale for the chosen primary endpoint is that the change in FVC is a universally accepted measure of disease severity, predictor of progression and associated with mortality risk in patients with pulmonary fibrosis.[8,17,19] Secondary endpoints were included to assess clinically relevant measures of FHP severity, progression and mortality.

In summary, the high morbidity and mortality risk of FHP underscores the need to explore new pharmacologic approaches to managing this devastating disease. Outcomes from this trial will provide valuable data on this antifibrotic agent's role as an add-on treatment in FHP and yield information that will inform future trials. Additionally, the design will allow the collection of biospecimens and collaborative mechanistic studies that will hopefully advance our understanding of FHP progression's pathobiology.

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Table 1. Entry criteria

Inclusion Criteria

Multidisciplinary Consensus Diagnosis of FHP

- Age 18 to 80 years at randomization.
- Diagnosis of FHP, defined from the first instance in which a patient was informed of having FHP for at least 3 to 6 months.
- HRCT according to pre-specified criteria:
  - Typical FHP[a]: Evidence of lung fibrosis (reticular abnormality and/or, traction bronchiectasis and/or, architectural distortion, and/or honeycombing) with either of the following:
    - Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones.
    - Inspiratory mosaic attenuation with three-density sign.

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

    AND
    - Lack of features suggesting an alternative diagnosis.
  - Indeterminate FHP[c]: CT signs of fibrosis without other features suggestive of HP and lack of features suggesting an alternative diagnosis.

FHP Disease Severity and Progression

- FVC ≥40%, DLCO ≥30% based either on historical pulmonary function tests obtained within the 60 days prior to Day 1.
- Presence of fibrotic abnormalities involving ≥5% of the lung parenchyma, with or without traction bronchiectasis or honeycombing, on high-resolution CT scan.
- Evidence of disease progression: worsening respiratory symptoms and increased extend of fibrosis on HRCT or relative decline in the FVC of at least 5% over 24 months.
- Able to walk ≥100 m during the 6-minute walk test at Screening.

Informed Consent and Protocol Adherence

- Able to understand and sign a written informed consent form.
- 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

Exclusion Criteria

Disease-Related Exclusions

- Not a suitable candidate for enrollment or unlikely to comply with the requirements of this study, in the opinion of the investigator
- Cigarette smoking at Screening or unwilling to avoid tobacco products throughout the study
- Known explanation for the interstitial lung disease, including but not limited to radiation, drug toxicity, sarcoidosis, pneumoconiosis.
- Clinical diagnosis of any connective tissue disease, including but not limited to scleroderma, polymyositis/dermatomyositis, and rheumatoid arthritis.
- Expected to receive a lung transplant within 6 to 12 months from randomization or on a lung transplant waiting list at randomization.
- 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

- Any condition other than FHP that, in the opinion of the investigator, is likely to result in the death of the patient within 6 to 12 months.
- Any condition that, in the opinion of the investigator, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone.
- 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).
- History of ongoing alcohol or substance abuse.
- History of severe hepatic impairment or end-stage liver disease.
- History of end-stage renal disease requiring dialysis.
- Clinical evidence of active infection including, but not limited to, bronchitis, pneumonia, sinusisits, or urinary tract infection.
- Unstable or deteriorating cardiac disease, including but not limited to the following:
  - Unstable angina pectoris or myocardial infarction.
  - Congestive heart failure requiring hospitalization.
  - Uncontrolled clinically significant arrhythmias.

Laboratory Exclusions

- 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 x ULN; alkaline phosphatase >2.5 x ULN within past 30 days.
- Creatinine clearance <30 mL/min, calculated using the Cockcroft-Gault formula within past 30 days.
- Electrocardiogram with a QTc interval >500 msec at Screening.

Medication Exclusions

- Prior use of pirfenidone, nintadinib or known hypersensitivity to any of the components of study treatment.
- Introduction, increase or escalation of immunosuppressive pharmacological therapy within 1 month (e.g. prednisone, azathioprine, mycophenolic acid and mycophenolate mofetil).*
- Use of any of the following therapies within 28 days before screening: bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, methotrexate, tacrolimus, tetrathiomolybdate, TNF-α inhibitors, imatinib mesylate, Interferon gamma-1b, and tyrosine kinase inhibitors, Fluvoxamine, Sildenafil (daily use).

In all subjects with biopsy specimens, data on the overall histological pattern and individual features will be determined and scored by an expert chest pathologist using a standardized data collection form. In the absence of surgical lung histology, a high-confidence provisional diagnosis based on the above CT confidence pattern and multidisciplinary consensus required:

a. These patients are required to have an identifiable antigen exposure, or 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. 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. 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.

* Decreasing or tapering off oral corticosteroids is allow.

Table 2. Endpoints

Primary Endpoint

- Mean change from baseline to week 52 in %FVC.

Secondary Endpoints

- Progression-free survival defined as the time from study treatment randomization to the first occurrence of any of the following events:
  - Relative decline from baseline in ≥10% in FVC and/or DLCO.
  - 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:
    - Increase from baseline FIO2 ≥1 L O2.
    - Clinically significant worsening of dyspnea and/or cough.
    - New, superimposed ground-glass opacities or consolidation or new alveolar opacities on chest x-ray or CT.
    - 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).
  - A decrease from baseline of at least 50 meters in 6-minute walk distance.
  - 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).
  - Death.
- Slope of FVC over 52-week treatment period.
- Mean change in %DLCO at week 52.
- Proportion of patients with all-cause mortality.
- Proportion of patients with all-cause hospitalization.
- Proportion of patients with hospitalization for respiratory cause.
- Proportion of patients with respiratory exacerbations requiring hospitalizations.
- Proportion of patients with evidence of progression in fibrosis on visual comparison of baseline and week 52 HRCT scans.

Exploratory Endpoints

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

Safety Endpoints

- Proportion of patients with treatment-emergent adverse events.
- Proportion of patients with treatment-emergent serious adverse events.
- Proportion of patients with treatment-emergent adverse drug reaction.
- Proportion of patients with treatment-emergent serious drug reaction.
- Proportion of patients with adverse events leading to early discontinuation of study treatment.

- Proportion of patients with treatment-emergent deaths.
- Proportion of patients with treatment-emergent changes in clinical laboratory findings and ECGs.

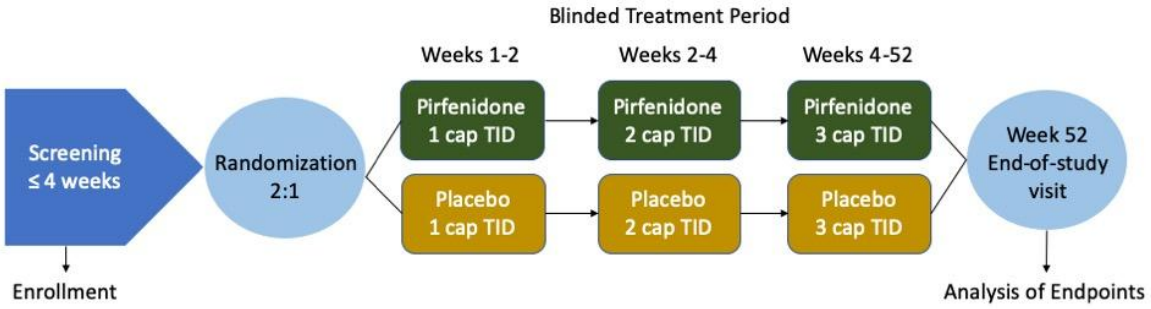

Figure 1. Trial design.