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Design of the MIST study: a double-blind, randomised, placebo-controlled phase 2b trial of pirfenidone solution for inhalation in patients with progressive pulmonary fibrosis

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ABSTRACT

Introduction Progressive pulmonary fibrosis (PPF) is a debilitating progression of pulmonary fibrosis in patients with interstitial lung diseases (ILDs) other than idiopathic pulmonary fibrosis (IPF). Oral pirfenidone has been studied in non-IPF ILDs, but in smaller academic studies, it did not achieve a statistically significant change in the primary endpoint. Increased systemic exposure with oral administration may lead to substantial adverse events and limit its utility. Clinical data support inhaled pirfenidone for the treatment of PPF with improved tolerability compared with orally administered pirfenidone.

Methods and analysis Approximately 300 patients with PPF will be randomised 2:1:2 to one of three treatment arms: AP01 100 mg two times per day, AP01 50 mg two times per day or placebo two times per day by oral inhalation using the investigational eFlow Nebuliser System (PARI Pharma GmbH, Germany). The primary endpoint is the change from baseline in forced vital capacity at week 52. The main secondary endpoints are change in quality of life measurements from baseline to 52 weeks, time to disease progression and change in lung fibrosis scores based on high-resolution CT from baseline to 52 weeks.

Trial registration number NCT06329401.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Progressive pulmonary fibrosis (PPF) is characterised by worsening fibrotic changes, increased symptoms and physiological decline over 12 months despite standard therapy. Oral pirfenidone, an antifibrotic approved by the Food and Drug Administration for use in idiopathic pulmonary fibrosis, may have a role in treating PPF, though it can cause dose-limiting adverse events.

WHAT THIS STUDY ADDS

⇒ The MIST study is the first randomised, double-blind, placebo-controlled trial to evaluate the safety and efficacy of inhaled pirfenidone (AP01) in patients with PPF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Targeted delivery of AP01 is expected to reduce systemic exposure and achieve better tolerability than oral pirfenidone, while maintaining or improving therapeutic effect in patients with PPF.

INTRODUCTION

Progressive pulmonary fibrosis (PPF) is a chronic condition in patients with interstitial lung disease (ILD). PPF was first formally defined in 2022 by international consensus based on the need to address the progression of pulmonary fibrosis (PF) in patients with ILDs other than idiopathic PF (IPF). The American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Asociación Latinoamericana de Tórax recommended an update to the prior IPF clinical practice guidelines, including creating and defining PPF. Based on the consensus, PPF is characterised by worsening fibrotic changes on CT imaging, increased symptoms and physiological decline over 12 months despite standard therapy.[1 2] It is estimated that 30–40% of patients with ILD will develop PPF over the course of their disease, equating to approximately 180 000 patients with PPF worldwide.[3 4] Nintedanib is currently the only therapy approved by the Food and Drug Administration (FDA) for the treatment of PPF.[5–8] Although pirfenidone is not approved for PPF, its antifibrotic mechanism of action, established efficacy in IPF and supportive off-label use provide a strong biological rationale for its potential role in PPF.[9] Clinical data specific to PPF are still

emerging, but early evidence supports further investigation and development. Although both nintedanib and pirfenidone demonstrate efficacy for IPF and PPF, both are also associated with dose-limiting toxicities/adverse events (AEs). Almost three-quarters of patients receiving orally administered pirfenidone experienced AEs, and in some, more than 80% discontinued within 3 years of initiating the drug, emphasising a significant clinical need for new approaches.[10]

AP01, an inhaled formulation of pirfenidone that is delivered using the eFlow Nebuliser System (PARI Pharma, Germany; hereafter referred to as eFlow), was developed to address the limitations of oral administration of pirfenidone. The predicted peak lung concentration for AP01 100 mg nebulised two times per day will be higher than that of the licensed dose of oral pirfenidone, and the pirfenidone systemic exposure following dosing with 100 mg two times per day of AP01 will be lower compared with the oral dose of 801 mg three times a day. In clinical studies to date, AP01 has been well tolerated, and the most common dose-limiting AEs associated with oral pirfenidone were diminished or ameliorated.[11] Moreover, in two trials involving patients with IPF, those receiving AP01 showed less decline in forced vital capacity (FVC) per cent predicted at 24 weeks compared with the historical rates of placebo groups in other studies, with average lung function near-stable at 48 weeks.[11 12]

MIST is a Phase 2b study evaluating the safety, efficacy and pharmacokinetics (PK) of multiple doses of AP01 compared with placebo, on top of standard of care, over 52 weeks in patients with PPF. Patients on background, stable dose antifibrotic therapy with nintedanib will be allowed to participate, but they will represent no more than 30% of the total randomised. Oral pirfenidone will not be allowed in this study. The primary objective is to evaluate the change from baseline in FVC at week 52 in the AP01 treatment groups as compared with placebo. In addition, efficacy will be measured in secondary endpoints of change from baseline in quality of life (QoL) measured using the Living with Pulmonary Fibrosis (LPF) questionnaire, time to disease progression and change in fibrosis scores via quantitative high-resolution CT (HRCT). Safety outcomes include the incidence of AEs, serious AEs, treatment-emergent deaths, bronchospasm caused by nebulisation of study drug and changes from baseline in clinical laboratory tests and ECG patterns. It is anticipated that the profile of AP01 will provide improved efficacy and better tolerability than oral pirfenidone, potentially preventing the progression of fibrosis and preserving lung function for a longer period of time.

METHODS AND ANALYSIS

Study design and oversight

The MIST study (ClinicalTrials.gov: NCT06329401, protocol dated 23 September 2024, V.2.2) is a randomised, double-blind, placebo-controlled clinical study to evaluate the safety and efficacy of two doses of AP01 (50 mg and 100 mg two times per day) versus placebo, on top of standard of care, in patients with PPF over 52 weeks. Patients, investigators, sponsor study team and all site personnel will be blinded to study drug. Study drug and matching placebo will be packaged the same and will be identical in appearance and taste. The study was designed with input from patients with PPF. The study is being conducted at ~150 sites in 14 countries and began in June 2024, with estimated completion in 2026.

Patients will enter a screening period of up to 4 weeks to assess eligibility, electronic diary (eDiary) compliance, eFlow training and to receive at least 1 week of open-label nebulised saline to establish a baseline for cough. Baseline stability of FVC will be evaluated before beginning study drug as a reference for all subsequent comparisons. Patients will complete additional in-clinic assessments at baseline and weeks 2, 4, 8, 12, 18, 26, 38, 48 and 52 and a follow-up telephone call at week 54. Patients will be encouraged to take all background maintenance respiratory medications at home per their normal routine prior to each study visit. At the completion of the study, patients may continue to receive AP01 by enrolling in an optional open-label extension (figure 1).

The study will be conducted in accordance with Good Clinical Practice (GCP). These standards respect the following guidelines: Guideline for GCP (R1): Consolidated Guideline (ICH, May 1996), US code of federal regulations (CFR) dealing with clinical studies (21 CFR Parts 50, 54, 56 and 312) and the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Written informed consent reviewed and approved by an institutional review board or independent ethics committee will be obtained from all participants.

Source documents for this study will include hospital records, procedure reports and data collection forms. These documents will be used to enter data on the case report forms (CRFs). Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. The sponsor is responsible for implementing and maintaining quality control and quality assurance systems with written Standard Operating Procedures to ensure that studies are conducted and data are generated, documented and reported in compliance with the protocol, accepted standards of GCP and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

On all study-specific documents other than the signed consent, as well as in the electronic database, the subject will be referred to by a randomly assigned study subject identification code. The key which links study subjects' codes to their identifiable data will be accessible only to those study site personnel who have a need to know such information and have been specifically authorised by the study site to access the key for purposes of performing certain functions in connection with the study. The key

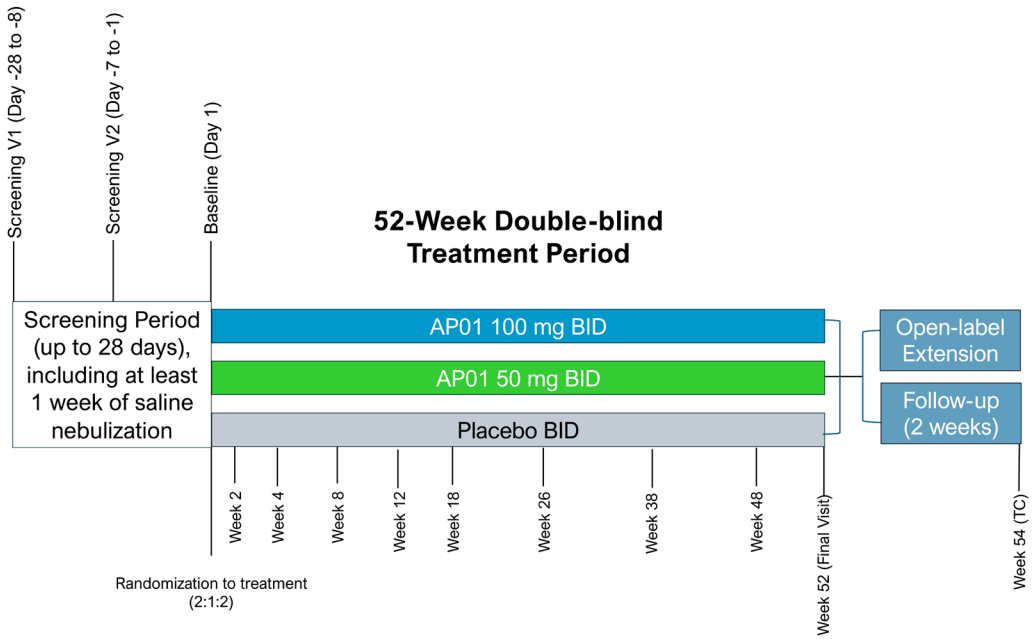


Figure 1 MIST study design. BID, two times per day; TC, telephone call; V, visit.

will be stored in a secure, confidential manner by the study site. Access to subjects' directly identifying personal information (such as a subject's name) will be restricted to the study doctor/collaborators, relevant health authorities (such as the US FDA and foreign health authorities), the Institutional Review Board or ethics committee, the sponsor and/or personnel authorised by the sponsor (eg, study monitors or auditors), when required to check the data, study procedures and compliance with GCP guidelines. All parties will comply with all applicable laws to ensure protection of participant data.

Patient population

Male and female patients aged ≥18 years will be eligible if they meet at least one of the following criteria for progression of ILD within the 24 months prior to screening: a relative decline in the FVC of at least 10% of the predicted value; a relative decline in the FVC of ≥5% to <10% of the predicted value accompanied by worsening of respiratory symptoms or an increased extent of fibrosis on HRCT; or worsening of respiratory symptoms and an increased extent of fibrosis on HRCT. At the time of screening, patients will be required to have an FVC >45% of the predicted value, a forced expiratory volume in 1 s (FEV_1)/FVC ≥0.7 or ≥age-adjusted lower limit of normal Global Lung Function Initiative (GLI) values,[13] and a diffusing capacity of the lung for carbon monoxide (DL_{CO}) (corrected for haemoglobin (Hb)) of ≥30% of the predicted value. Eligible patients are also required to have fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis, with or without honeycombing, with a disease extent of >10%. HRCT characteristics will be used to classify patients as having a usual interstitial pneumonia (UIP)-like fibrotic pattern or other fibrotic patterns (based on central review) (box 1). Exclusion criteria include a diagnosis of IPF, significant clinical worsening of PPF between screening and the baseline visit, current treatment with oral pirfenidone or within 3 months prior to screening, advanced liver or kidney disease and medical conditions including cardiovascular disease, pulmonary arterial hypertension or likely lung transplant within 12 months (box 1).

Prior, concomitant and prohibited medication

Patients receiving standard of care with nintedanib must have been on treatment for at least 6 months prior to screening with or without dose adjustments and/or drug interruptions during that period and who have met all other inclusion criteria. Patients currently on a stable dose of nintedanib are allowed to stop taking nintedanib at the discretion of the Investigator while remaining on study drug and in the study. Patients who have discontinued nintedanib prior to screening must have been off nintedanib for a minimum of 12 weeks. At any time in the study, if disease progression is noted and the patient is not taking nintedanib as part of their standard of care, the investigator will determine whether it is in the patient's best interest to initiate nintedanib. In these situations, the study drug will continue to be administered as per the protocol.

Patients already on mycophenolate mofetil (MMF), tocilizumab, methotrexate, azathioprine, oral corticosteroid (prednisone ≤20 mg or equivalent allowed) or rituximab must have been on these treatments for 12 weeks prior to Screening (6 months for rituximab) with or without dose adjustments and/or drug interruptions during that period. Patients who have discontinued MMF or tocilizumab prior to screening must have been off

Box 1 Patient eligibility

Key inclusion criteria

PPF diagnosis

In subjects with interstitial lung disease (ILD) of known or unknown aetiology other than idiopathic pulmonary fibrosis (IPF) who have radiological evidence of pulmonary fibrosis, progressive pulmonary fibrosis (PPF) is defined as:

⇒ Physiological evidence of progression within at least 1 of the following criteria despite treatment with approved or unapproved medications commonly used in practice (per Investigator):
- Relative decline in forced vital capacity (FVC) ≥10% predicted within the previous 24 months compared with Screening Visit 1.
- Relative decline in FVC ≥5 to <10% predicted within the previous 24 months compared with Screening Visit 1 with at least 1 of the 2 following criteria:
  - Worsening respiratory symptoms (note: changes attributable to comorbidities, eg, infection, heart failure must be excluded) OR
  - Radiological (high-resolution CT (HRCT)) evidence of disease progression per a local or central radiologist, for example:
    - Increased extent or severity of traction bronchiectasis and bronchiolectasis.
    - New ground-glass opacity with traction bronchiectasis.
    - New fine reticulation.
    - Increased extent or increased coarseness of reticular abnormality.
    - New or increased honeycombing.
    - Increased lobar volume loss.
- Worsening of respiratory symptoms (note: changes attributable to comorbidities, eg, infection, heart failure must be excluded) AND radiological (HRCT) evidence of disease progression per a local or central radiologist.

Pulmonary function test criteria at screening visit:

⇒ FVC ≥45% of predicted normal at Screening Visit 1.

⇒ Forced expiratory volume in 1 s (FEV_1)/FVC ≥0.7 or ≥age-adjusted lower limit of normal Global Lung Function Initiative values at Screening Visit 1.

⇒ Diffusing capacity of the lung for carbon monoxide (DL_{CO}) ≥30% of predicted, corrected for haemoglobin at Screening Visit 1.

⇒ Acceptability: subject can perform acceptable spirometry (ie, meet American Thoracic Society (ATS)/European Respiratory Society (ERS) acceptability criteria at both Screening Visits).

Note: spirometry (including DL_{CO}) obtained at Visit 1 may be repeated to confirm eligibility once, if discussed and approved by the Medical Monitor (eg, technical issue, subject fatigue).

⇒ Fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, on an available HRCT scan within the past year.
- If the subject does not meet this criterion, but the HRCT scan is >6 months old and the Investigator considers the subject's disease has progressed, then an HRCT will be obtained to reassess eligibility.
- If the subject does meet this criterion with the historical HRCT but the HRCT is more than 12 weeks prior to Screening Visit 1, an HRCT will be performed during the screening period to use as baseline, in countries where feasible.

Note: CT results must be confirmed through the central over-read process.

Continued

Box 1 Continued

Prior therapy

⇒ For subjects already on nintedanib (up to 30% of subjects): must have been on nintedanib for at least 6 months prior to Screening with or without dose adjustments and/or interruptions.

⇒ For subjects who have discontinued nintedanib prior to Screening: must have been off nintedanib for a minimum of 12 weeks.

⇒ For subjects treated with rheumatoid arthritis/connective tissue disease (RA/CTD) drugs for non-pulmonary manifestations of RA/CTD, they must have been on these treatments for 12 weeks prior to Screening.

⇒ For subjects already on mycophenolate mofetil (MMF), tocilizumab, methotrexate, azathioprine, oral corticosteroids or rituximab: must have been on these medications for at least 3 months prior to Screening (6 months for rituximab).

⇒ For subjects who have discontinued MMF or tocilizumab prior to Screening: must have been off these medications for a minimum of 12 weeks.

⇒ For subjects who have discontinued rituximab prior to Screening: must have received the last dose of rituximab at least 6 months prior to Screening.

Other

⇒ Estimated minimum life expectancy of at least 12 months for non-PPF-related disease in the opinion of the Investigator.

⇒ Subject and Investigator considered all medicinal treatment options and/or possibly lung transplantation prior to considering participation in the study.

⇒ Male subjects and female subjects of childbearing potential (defined as females who are fertile, following menarche and until becoming postmenopausal unless permanently sterile) agree to use highly effective contraception measures from the time of first dose of study drug (for the male subject) or the signing of the informed consent form (ICF) (for the female subject), during the study and until 90 days after the last dose of study drug. Subjects agree not to donate eggs or sperm during the same period. Male subjects must use a condom and female partners of male subjects who are of childbearing potential must use a highly effective method of contraception, defined below:
- A highly effective method of contraception is one that results in a low failure rate (ie, <1% per year) when used consistently and correctly. The acceptable methods of contraception include: sexual abstinence (defined as refraining from heterosexual intercourse during the entire treatment and follow-up periods), a vasectomised partner, bilateral tubal occlusion, any effective intrauterine device/hormone-releasing system and progesterone-only (oral, injectable or implantable) or combined (oestrogen-containing and progesterone-containing; oral, intravaginal or transdermal) hormonal contraception associated with inhibition of ovulation. Note: periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only and lactational amenorrhoea method are not acceptable methods of contraception.
- The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the drug absorption may be reduced. Advise women taking oral hormonal contraceptives experiencing these conditions to use alternative highly effective contraception.

Note: permanent sterilisation methods include hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy. A postmenopausal

Continued

Box 1 Continued

state is defined as no menses for 12 months without an alternative medical cause. In the absence of 12 months of amenorrhoea, a single follicle-stimulating hormone measurement is insufficient to document menopause.

⇒ Females of non-childbearing potential who are physiologically incapable of becoming pregnant, including any female who is 2 years postmenopausal.

Key exclusion criteria

A subject who meets any of the following criteria will be excluded from this study:

⇒ Current treatment with oral pirfenidone or treatment with oral pirfenidone within 3 months prior to Screening.

⇒ Elevated liver enzymes and liver injury at Screening defined as:
- Alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal (ULN), OR
- Bilirubin >2.0 × ULN.

⇒ Renal disease with a creatinine clearance <30 mL/min, calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula (Inker *et al*, 2021). Retesting is allowed once.

⇒ Diagnosis of IPF is based on the ATS diagnostic algorithm for IPF. Usual interstitial pneumonia that is not idiopathic, for example, related to RA, familial ILD or other is not exclusionary.

⇒ Greater extent of emphysema than of fibrotic ILD on HRCT. Note: CT results must be confirmed through the central overread process.

⇒ Significant clinical worsening of PPF between Screening Visit 1 and Visit 3 (week 0/Day 1/randomisation), as assessed by the Investigator.

⇒ History of acute respiratory exacerbation requiring hospitalisation within 12 weeks prior to Screening or at any time during the Screening Period.

⇒ In the opinion of the Investigator, Group 1 pulmonary arterial hypertension is present as evidenced by any of the following:
- Mean pulmonary artery pressure ≥20 mm Hg on right heart catheterisation.
- Cardiac index ≤2 L/min/m^2 on right heart catheterisation.
- The use of any prostacyclin therapy, IP receptor agonist, endothelin-receptor antagonist or phosphodiesterase-5 inhibitor or soluble guanylate cyclase stimulator within 60 days prior to baseline (Visit 3).

⇒ Subjects who cannot meet protocol-specified baseline stability criteria. FVC baseline stability is defined as the FVC assessments at Visit 3 being within ±12% of the mean of the FVC assessments obtained at the 2 preceding visits. At Visit 3, if the predose FVC is outside of ±12% range, the subject will not be randomised and will be considered a screen failure.

⇒ Major extrathoracic physiological restriction (eg, neuromuscular disease).

⇒ In the opinion of the Investigator, other clinically significant pulmonary or pleural abnormalities.

⇒ Cardiovascular diseases, any of the following:
- Severe hypertension (systolic blood pressure (SBP) >180 mm Hg and/or diastolic blood pressure (DBP) >110 mm Hg), and subjects with severe hypotension (SBP <90 mm Hg and/or DBP <50 mm Hg), within 3 months of Screening Visit 1.
- Hypertension or hypotension is considered not controlled in line with clinical standards.
- Myocardial infarction within 6 months of Screening Visit 1.

Continued

Box 1 Continued

- Unstable cardiac angina within 6 months of Screening Visit 1.
- Class IV New York Heart Association chronic heart failure.

⇒ Corrected QT interval (QTc; using Fridericia's (QTcF) formula) of >470 ms at Screening Visit 1.

⇒ Severe hepatic impairment per the Child-Pugh scoring system (Class C) or end-stage liver disease.

⇒ History of malignancy within the past 5 years (except for carcinoma in situ of the uterine cervix, basal cell carcinoma of the skin that has been treated with no evidence of recurrence, prostate cancer that has been medically managed through active surveillance or watchful waiting, squamous cell carcinoma of the skin if fully resected, non-invasive ductal carcinoma in situ of the breast and melanoma in situ).

⇒ Subjects likely to undergo a single or double lung transplant within 12 months.

⇒ Unstable asthma or chronic obstructive pulmonary disease (requiring oral corticosteroids for an exacerbation in the previous 3 months).

⇒ Active infection requiring systemic antibiotics (eg, bronchitis, pneumonia, sinusitis, urinary tract infection, cellulitis) that in the opinion of the Investigator is clinically significant within 4 weeks of Screening and at any time throughout the Screening Period.

⇒ Subject with a positive test for HIV, hepatitis B virus or hepatitis C virus at Screening Visit 1.

⇒ Any chronic or clinically significant medical condition that, in the opinion of the Investigator, would jeopardise the safety or rights of the subject.

⇒ Current smokers or prior smokers who have smoked within the past 3 months before Screening.

⇒ Women who are pregnant, nursing or who plan to become pregnant while in the study.

⇒ Non-compliance: subjects unable to comply with study procedures including non-compliance with diary completion (ie, <70% subject completion of diary assessments in the last 7 days preceding Visit 3).

⇒ Subjects who have symptoms of bronchospasm (eg, wheezing, chest pain or tightness, coughing, fatigue or dizziness) and a decline in FEV_1 of at least 20% after saline nebulisation during the Screening Period. At the discretion of the Investigator, a marked increase in cough following saline nebulisation may also constitute exclusion from participation in the study.

⇒ Not a suitable candidate for enrolment or unlikely to comply with the requirements of this study, as assessed by the Investigator.

⇒ Previous participation in an AP01 study. Participation in a concurrent clinical study or in a clinical study in which an investigational drug product was administered within the previous 30 days, or five half-lives of the previously administered investigational product, whichever is shorter. Note: subjects in registry studies can be included in this study.

these medications for a minimum of 12 weeks. Patients who have discontinued rituximab prior to Screening must have received the last dose of rituximab at least 6 months prior to Screening.

Current use of oral pirfenidone, any other investigational therapy and nicotine or tobacco-containing products is prohibited during the study. However, nicotine patches and nicotine gum are permitted during the study. Illicit drugs or drugs of abuse will not be allowed, with

the exception of medical marijuana taken orally if used for medical purposes (and allowed by local and regional regulations), provided there is no change in the dose or frequency of consumption. Patients are encouraged to be vaccinated in compliance with local and regional requirements, including the recommendations on the COVID-19, influenza and pneumococcal vaccines.

Randomisation and stratification

Up to 300 eligible patients will be randomised and stratified by background use of oral nintedanib at baseline (capped at 30%) and UIP-like pattern on HRCT (capped at 62%) in a 2:1:2 ratio to one of three treatment arms: AP01 100 mg two times per day, AP01 50 mg two times per day or placebo two times per day. Randomisation will be centralised through the use of an interactive web response system (IWRS). In this study, the IWRS is used to control all drug distribution and inventory. Both AP01 and placebo will be administered by oral inhalation via eFlow. Enrolment will also be capped at 45% of patients with other fibrotic patterns (ie, not UIP-like patterns) on HRCT. The sample size is based on the following assumptions: change from baseline in FVC is normally distributed, the mean difference in the primary endpoint between each AP01 group and placebo is 100 mL at week 52, the SD of change from baseline in FVC at week 52 is 225 mL and the rate of study discontinuations is 10% by week 52. Under these assumptions, the nominal power of the t-test to detect difference from placebo is 90% and 75% for the AP01 100 mg two times per day and AP01 50 mg two times per day group, respectively. A blinded sample size reassessment is planned to ensure the validity of the variability assumption.

Study endpoints

Primary endpoint

The primary endpoint of the study is the change from baseline in FVC (mL) at week 52. Spirometry will be conducted up to a maximum of eight times to obtain three acceptable manoeuvres, meeting American Thoracic Society/European Respiratory Society spirometry criteria. Spirometry readings will be taken within 60 min predose of saline at screening visits 1 and 2, predose of study drug at baseline through week 48 and on the morning of the week 52 visit. At baseline and week 4, serial spirometry will also be taken between 30 and 60 min, 2 hours and 4 hours postdose of study drug. For the serial postdose spirometry, the key endpoint is a change from baseline in FEV_1 (box 2).

Secondary endpoint

Secondary endpoints include change from baseline at week 52 in QoL using the LPF questionnaire, quantitative lung fibrosis score on HRCT and time to disease progression. Disease progression is a composite assessment based on the time to documented decline of ≥10% in absolute FVC per cent predicted or occurrence of respiratory hospitalisation, lung transplant or all-cause death prior to week 52 (box 2).

Box 2 Endpoints

Primary endpoint

⇒ Change from baseline in forced vital capacity (FVC) (mL) at week 52.

Secondary endpoint

⇒ Change from baseline in quality of life measurements as assessed by Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire total score at week 52.
⇒ Time to disease progression. Disease progression is defined as absolute FVC per cent predicted decline of ≥10% prior to week 52.
⇒ Change in lung fibrosis score based on high resolution CT from baseline to 52 weeks.

Exploratory endpoints

⇒ Annual rate of decline in FVC (mL) over 52 weeks.
⇒ Time to adjudicated death over 52 weeks.
⇒ Total number of adjudicated respiratory deaths over 52 weeks.
⇒ Time to adjudicated death due to respiratory cause over 52 weeks.
⇒ Time to first adjudicated acute progressive pulmonary fibrosis (PPF) exacerbation over 52 weeks.
⇒ Total number of adjudicated acute PPF exacerbations over 52 weeks.
⇒ Time to first adjudicated respiratory hospitalisation over 52 weeks.
⇒ Time to disease progression, including respiratory hospitalisation, lung transplant and/or death.

Safety

⇒ Adverse events (AEs) and serious AEs.
⇒ Deaths.
⇒ Vital signs, physical examination, body weight.
⇒ Clinical laboratory tests (haematology, serum chemistry, urinalysis and urinary creatinine clearance).
⇒ ECG pattern.
⇒ Bronchospasm.

Pharmacokinetic

⇒ Increase in maximum concentration (C_{max}) and trough concentration of pirfenidone and its metabolites (5-carboxy pirfenidone and 5-hydroxy pirfenidone) at week 4, after repeated administration, in all subjects.
⇒ In a subgroup of subjects, increase in C_{max} and area under the curve of pirfenidone and its metabolites (5-carboxy pirfenidone and 5-hydroxy pirfenidone) at week 4.
⇒ Influence of covariates, including gender, body weight, smoking and comedication on the systemic exposure to pirfenidone and its metabolites (5-carboxy pirfenidone and 5-hydroxy pirfenidone), in all subjects.

Exploratory endpoints

Exploratory endpoints include time to first and number of acute PPF exacerbations, time to first adjudicated respiratory hospitalisation, absolute changes in DL_{CO}, cough severity and patient-reported outcomes for all enrolled patients. A PPF exacerbation is defined as an acute, clinically significant respiratory deterioration characterised by evidence of new, widespread alveolar abnormality and an acute respiratory deterioration in PPF (typically <1 month in duration). New radiographic abnormalities

(bilateral ground glass opacification or consolidation on HRCT) cannot be fully explained by cardiac failure or fluid overload.[14] The number of PPF exacerbations and time to the first acute PPF exacerbation will be measured over 52 weeks.

Respiratory hospitalisation has been demonstrated to be an important endpoint in clinical trials and associated with time to death from any cause in IPF, a closely related ILD.[15–17] The Adjudication Committee will confirm whether the cause of hospitalisation was due to a respiratory cause. Time to first and rate of respiratory hospitalisation will be measured; respiratory hospitalisations for PPF worsening will also be measured as part of the composite clinical outcome.

DL_{CO} will be measured using the single-breath technique according to the American Thoracic Society/European Respiratory Society guidelines[18] and will be collected at screening, baseline, week 26 and week 52. Predicted DL_{CO} corrected for Hb expressed in g/dL will be calculated as predicted DL_{CO} corrected for Hb=Predicted DL_{CO} × (1.7Hb)/(10.22+Hb) for males and predicted DL_{CO} corrected for Hb=Predicted DL_{CO} × (1.7Hb)/(9.38+Hb) for females. The DL_{CO} will be based on the GLI reference equation. DL_{CO} will be measured on the site's own device, with the data to be entered into the provided spirometry system for central data review.

Cough severity will be assessed using the cough severity numerical rating scale instrument, a single-dimension 11-point Likert scale ranging from 0 ('no cough') to 10 ('worst possible cough').[19 20] Assessments will be made in the clinic at predose and 30–60 min postdose following saline administration during the screening period and following study drug administration during the treatment period at weeks 4, 26, 48 and 52.

The following patient-reported outcomes will be used to assess QoL and disease-related symptoms: LPF and Leicester Cough Questionnaire (LCQ). The LPF questionnaire is a 44-item questionnaire with two modules: (1) symptoms (23 items) and (2) impacts (21 items). The LPF was developed with the input of patients with PF and thus is intended to capture perceptions specific to patients with PF.[21] The LCQ is a health-related QoL measure of chronic cough.[22] The LCQ total score ranges from 3 to 21 and from 1 to 7 for physical, psychological and social domains; a higher score indicates a better health-related QoL. The LPF and LCQ will be self-administered by the patient at screening, baseline and at the week 12, 26, 38 and 52 visits (box 2).

Safety

AEs for all patients will be coded by using the current version of the Medical Dictionary for Regulatory Activities. Safety assessments will include monitoring for changes from baseline vital signs assessments, physical examination, body weight and laboratory evaluations, and ECG parameters will be summarised by visit and by treatment group. Per protocol, investigators will monitor for abnormal liver biochemistry based on elevations in aspartate aminotransferase and/or alanine aminotransferase in combination with elevated bilirubin, elevated international normalised ratio or new or worsening hepatic-related symptoms. Relevant parameters must be observed at the same visit or within approximately 30 days of each other. The frequency of subjects with safety laboratory results outside of normal reference ranges will be tabulated by treatment and visit. Cough may occur after inhalation of aerosol product, including saline, and as a general symptom of PPF. Patients will be monitored for cough and possible additional symptoms suggestive of bronchospasm (eg, wheezing, chest pain or tightness, fatigue or dizziness), and a ≥20% decrease in FEV_1 from the predose to postdose measurements on that specific test day. Symptoms of bronchospasm after study drug administration can be managed with a short-acting beta agonist (SABA). If felt necessary, patients may be pretreated with two puffs (90–100 µg) of SABA prior to subsequent study drug administrations. Patients who discontinue treatment due to bronchospasm will be encouraged to continue in the study and complete the remaining visits.

The sponsor will appoint an independent, external Data Safety Monitoring Board (DSMB) for the periodic review of available safety data. Members of the DSMB will review the safety data generated externally and independently of the sponsor at predetermined intervals to provide a systematic and unbiased assessment of safety data. If significant safety issues arise in between scheduled meetings, ad hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DSMB may recommend modification or termination of the study.

Pharmacokinetics

In all patients, blood samples for plasma PK analysis of pirfenidone and metabolites will be assayed using validated liquid chromatography with tandem mass spectrometry methods. Blood samples will be collected at week 0/Day 1/randomisation and week 4. On each occasion, a plasma sample will be collected prior to the dose and 10 min after completing administration of the dose. At select sites, additional PK sampling will be taken in a subset of up to 50 patients who will have plasma samples collected at predose, 10 min, 30 min, 2 hours, 4 hours and 6 hours postdose at week 0/Day 1/randomisation and week 4.

Statistical analysis

Continuous variables will be summarised by treatment group with descriptive statistics (eg, number of observations, mean, SD, median, IQR, maximum and minimum). Categorical variables will be tabulated by frequency and per cent of patients per dose group. The main estimand of interest for this study is Treatment Policy, which aims to evaluate the effect of intention to treat on patients with PPF with AP01, regardless of adherence to the planned course of treatment. The primary endpoint will be evaluated using a mixed model for repeated measures. This model will have change from baseline in FVC as the dependent variable, and

Table 1

Key elements to retain on the MIST design	
ID	AP01 (inhaled pirfenidone)
Patient population	~300 patients with PPF
Key inclusion criteria	PPF criteria within the 24 months before screening: ► FVC decline >10%. ► FVC decline ≥5% and <10% + worsening respiratory symptoms or HRCT evidence of disease progression. ► Worsening respiratory symptoms+HRCT evidence of disease progression. PFT criteria (FVC ≥45%; FEV1/FVC ≥0.7 age corrected for LLN; DL_{CO} ≥30%).
Concomitant medications	Background SOC nintedanib therapy (cap 30%)* Immunotherapy ► MMF, tocilizumab, MTX, azathioprine, oral corticosteroid (prednisone ≤20 mg or equivalent) for 12 weeks prior to Screening. ► Rituximab for 6 months prior to Screening.
Key exclusion criteria	IPF diagnosis. PPF clinical worsening.
Primary endpoint	Change from baseline in FVC at 52 weeks.

*Must have been on treatment for at least 6 months prior to screening with or without dose adjustments and/or drug interruptions during that period.
DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution CT; IPF, idiopathic pulmonary fibrosis; LLN, lower limit of normal; MMF, mycophenolate mofetil; MTX, methotrexate; PFT, pulmonary function test; PPF, progressive pulmonary fibrosis; SOC, standard of care.

treatment, visit, visit by treatment interaction, background use of oral nintedanib at baseline (yes or no), HRCT UIP-like fibrotic pattern (yes or no), need for oxygen, baseline DL_{CO}, age, gender and baseline FVC as explanatory variables. An unstructured covariance matrix will be used to model correlation within patient. The other change from baseline continuous endpoints will be analysed using a similar model. The time to disease progression will be analysed using a Cox proportional hazards model with the same explanatory variables used for the primary endpoint. All collected plasma concentration data for pirfenidone and its metabolites (5-carboxy pirfenidone and 5-hydroxy pirfenidone) will be tabulated and plotted by dose level for the PK and PK substudy sets. Concentration data will be summarised for day 1 and week 4 using descriptive statistics.

Demographic data and baseline characteristics will be summarised across the treatment groups. Efficacy evaluations will be performed using the full analysis set consisting of all randomised patients. Analyses will be based on observed data only; no data will be imputed. All statistical analyses will be performed using SAS V.9.4.

DISCUSSION

Despite advancements in understanding the biological mechanisms underlying PPF, the approved antifibrotic treatment options for PPF remain limited to one drug (nintedanib), which is associated with extensive side effects that are often dose-limiting.[10] The pathology and progression of PPF are similar to that of IPF. Pirfenidone, an approved drug for IPF, may show a treatment effect in both patient groups. However, like nintedanib, dosing-limiting side effects, including liver toxicities, gastrointestinal issues and skin reactions with oral pirfenidone, limit the utility of orally administered pirfenidone.[10] Inhaled AP01 directs pirfenidone to the lung and was well tolerated in phase 1b efficacy assessments, including improved FVC and QoL in patients with IPF, suggesting a promising profile for PPF.

The MIST phase 2b study is timely in light of the new PPF designation and the need for well-tolerated therapies. The MIST study design directly addresses criteria provided by the FDA, which set criteria for the consideration of how patients feel, function and survive, and by an international consortium of patients, clinicians and regulatory professionals who recommended endpoints that mirror patients' lived experiences.[2] The primary endpoint of the MIST study (change from baseline in FVC at week 52) was selected for objective functional assessments and to allow comparison with previously completed trials (INBUILD (Nintedanib in Progressive Fibrosing Interstitial Lung Diseases)).[8] Secondary and exploratory endpoints that measure QoL and time to disease progression, hospitalisation and lung transplant complement functional assessments to allow a more complete understanding of a patient's experience with the disease.

Clinical and mechanistic similarities, including activation and proliferation of fibroblasts and inflammation and associated pulmonary decline, across the clinical spectrum of PPF motivate the inclusion of patients with PPF of all aetiologies. A high mortality rate is observed, especially among those with declining FVC, UIP on HRCT, the extent of fibrosis and/or honeycombing on HRCT.[23] Patients with PPF experience a high disease burden with a relative paucity of effective treatments that lack significant dose-limiting AEs associated with orally administered treatments. New approaches are needed to minimise respiratory symptoms, frequent exacerbations and hospitalisations and early mortality, and clear consideration of conflicting or weak evidence with regard to pirfenidone effects in PPF is needed to clarify the role of pirfenidone in PPF.[7]

CONCLUSIONS

MIST will study the safety and efficacy of AP01 (inhaled pirfenidone) in patients with PPF over 52 weeks (table 1). In addition to the safety and efficacy endpoints, MIST will carefully examine the presence of cough in this population of patients. Cough in relation to a subject's PPF will be differentiated from a cough that may be observed during nebulisation

of study drug. Results will inform clinical management of PPF, may reduce negative side effects associated with pirfenidone and increase QoL in patients with PPF.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The trial is conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (GCP). This is a multicentre study with multiple local IRB/IEC approvals. In the USA, Advarra IRB is registered with OHRP and FDA under IRB#00000971. See online supplemental table 1 Study Sites and Institutional Review Boards/Ethics Committees for the full list of IRB/IEC names. Participants gave informed consent to participate in the study before taking part.

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