A Randomized Open-Label, Phase 1b Study of the Safety of Pirfenidone Solution for Inhalation (AP01) in Patients with Idiopathic Pulmonary Fibrosis (ATLAS Study)

Published: 20-12-2018
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Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50041

Source
ToetsingOnline

Brief title
ATLAS study

Condition

- Respiratory disorders NEC

Synonym
build-up of scar tissue in the lungs, Idiopathic pulmonary fibrosis (IPF)

Research involving
Human

Sponsors and support

Primary sponsor: Avalyn Pharma, Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Idiopathic Pulmonary Fibrosis, Open-Label, Phase 1b, Pirfenidone Solution for Inhalation (AP01)

Outcome measures

Primary outcome

* Treatment-emergent AEs

* Change from pre-dose to post-dose FEV1 after initial dose

* Treatment-emergent deaths

* Treatment-emergent changes in clinical laboratory findings

* Changes in vital signs

Secondary outcome

* Change from Baseline in FVC % predicted

* Change from Baseline in DLCO

* Change from Baseline in Patient Reported Outcomes (PRO)

* Change from Baseline in cough frequency and intensity

* Change from Baseline in extent of fibrosis and lung volumes

Study description

Background summary

Idiopathic pulmonary fibrosis (IPF) is a type of lung disease that results in scarring (fibrosis) of the lungs for an unknown reason. Over time, the scarring gets worse and it becomes hard to take in a deep breath and the lungs cannot take in enough oxygen.

Momentarily the study drug (pirfenidone solution for inhalation) is available as treatment for idiopathic pulmonary fibrosis, which is given in a capsule for oral use. However, studies have shown the use of oral pirfenidone leads to side effects in many patients and in some cases these side effects prevent the use of medication. A previous study has shown that a single dose of AP01 up to 100 mg given as an inhaled formulation was safe and well tolerated. It has shown that more pirfenidone was absorbed in the lungs which may lead to better efficacy as well as a reduction in the level of study drug which was absorbed by the blood which causes less side effects.

In this study we want to test the safety and tolerability of multiple doses. The results of this study will also be used for future research.

Study objective

The primary objective is to evaluate safety and tolerability of treatment with AP01.

This study will also evaluate the effect of AP01 on various efficacy measures as follows:
* To evaluate the safety and tolerability of treatment with AP01 when given either once or twice daily to patients with IPF;
* To estimate the treatment effect of AP01 given 50 mg once daily and 100 mg twice daily on absolute change in percent predicted FVC in patients with IPF;
* To estimate the treatment effect of AP01 given 50 mg once daily and 100 mg twice daily on absolute change in percent predicted Diffusion Capacity for Carbon Monoxide (DLCO) in patients with IPF;
* To compare the safety and efficacy of 50 mg once daily vs 100 mg twice daily dosing to provide guidance on dosing regimens for future studies;
* To estimate the treatment effect of AP01 given 50 mg once daily and 100 mg twice daily on change in Patient Reported Outcomes (PROs) and cough in patients with IPF;

Study design

This is a randomized, open-label study of Pirfenidone Solution for Inhalation (AP01) 50 mg once daily or 100 mg twice daily. This study has 2 parts.
Part A (24 weeks): Patients will be randomised in a 1:1 ratio to one of two treatment arms: 50 mg once daily or 100 mg twice daily. On Day 1, the initial dose of the drug will be administered in the clinic to confirm airway tolerance. If in the investigator*s opinion, the patient had tolerability issues during the first dose administration, a second dose, at least 4 hours later, will also be observed. The remainder of the doses will be administered by the patient outside of the clinic. Patients will have a telephone assessment at Week 1 and an in-clinic assessment at Weeks 4, 8, 12, 16, 20, and 24.

Patients who do not continue to Part B or who are withdrawn from the study prior to completion should return for an Early Termination visit. Week 4 safety data from the first 20 patients will be reviewed by a Data and Safety Monitoring Board (DSMB), who may suggest changes to design or stopping of the study based on safety concerns.

Part B (48 weeks): Patients who, in the opinion of the investigator, are compliant with study treatment dosing and study procedures will be permitted to enter Part B. All patients will continue to receive the treatment regimen (50 mg once daily or 100 mg twice daily) to which they were randomized in Part A. If one dosing regimen is determined to be superior either from an efficacy or safety standpoint, Part B may be converted to a single dose regimen. All patients who participate in Part B will be dosed with the selected regimen. Any patients already participating in Part B will be converted to the chosen single dose regimen at that time. Patients will have monthly telephone assessments and quarterly in-clinic assessments. All patients that complete the study visits through Part B will return for a Follow-up visit, 28 days after their End of Study visit.

Intervention

The research is divided into part A and part B. Part A lasts 24 weeks (approximately 6 months). Part B lasts 48 weeks (about 1 year).
Patients will be assigned to one of the following treatments:
* 50 mg AP01 once daily;
* 100 mg AP01 twice daily (at least 4 hours apart).

Study burden and risks

Please refer to table 5 and 6 in the protocol, page 40-42 (schedule of tests and events) for more information.

The research is divided into two parts, part A and B.
Part A lasts for 24 weeks (about 6 months). Patients are asked to come to the hospital every four weeks during this period.
Part B lasts 48 weeks (about 1 year). In this period, patients are asked to come to the hospital every 12 weeks and are contacted by telephone every month.

The first two visits (screening and visit 2) last about 3-4 hours. all other visits take about 1-2.5 hours.

During these visits the following tests and procedures will take place:
- Demographic and medical history (1 time)
- Physical exam, vital signs (13 times)
- ECG (1 time)
- CT scans of the Lungs (2 times)

- Questionnaires: Cough VAS, KBILD and LCQ (12 times)
- Blood and urine tests (13 times)
- Spirometry tests (including diffusing capacity (DLCO) test (5 extra times for this research)
- Patient will be asked to wear a Cough monitor for 24 hours and to complete a diary during this time (3 times during this study)
- Pregnancy tests in women of childbearing potential (12 times)
- Female patients: no breastfeeding allowed. Effective methods of birth control must be used from the time of signing the ICF, throughout the entire study and for 30 days following the last dose of the study drug.

Possible known side effects have been described in the IB, patient informed consent form and section E9 of this form.

Momentarily the study drug (pirfenidone) is available as treatment for idiopathic pulmonary fibrosis, which is given in a capsule for oral use. However, studies have shown the use of oral pirfenidone leads to side effects in many patients and in some cases these side effects prevent the use of medication. A previous study has shown that a single dose up to 100 mg/mL given as an inhaled formulation was safe and well tolerated. Inhalation provides higher levels of drug to the lungs and lower levels to the blood, which may improve efficacy and reduce side effects.
In this study we want to test the safety and tolerability of multiple doses.
The results of this study will also be used for future research.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male and female patients, at least 40 years of age at Screening
2. Not eligible for oral pirfenidone and nintedanib due to national formulary; restrictions OR intolerant to or unwilling to start oral pirfenidone and nintedanib, if previously offered;
3. Clinical symptoms consistent with IPF of * 12 months duration (with or without IPF diagnosis)
4. Diagnosis of IPF, defined as the first instance in which a patient was informed of having IPF, no more than 60 months before randomization;

Patients that have had an IPF diagnosis * 1 year, the following criteria must be met:
- HRCT and/or Surgical Lung Biopsy findings consistent with UIP. If honeycombing is not present on the HRCT, then one or both of the following criteria must be present:
* Disease progression since diagnosis by HRCT and/or
* An absolute loss of FVC * 5% percent predicted over the past 12 months,
Patients that have had IPF diagnosis within the last year, the following criteria must be met:
- Diagnosis of Usual Interstitial Pneumonia (UIP) or IPF by HRCT (HRCT must be performed within 12 months prior to Screening) and/or Surgical Lung Biopsy
5. Extent of fibrotic changes (honeycombing, reticular changes) greater than the extent of emphysema on HRCT scan, confirmed by central review;
6. No features supporting an alternative diagnosis on transbronchial biopsy, BAL, or surgical lung biopsy, if performed;
7. 40% * FVC * 90 % predicted at Screening based on Global Lung Initiative12 equations. The first 20 patients randomized must have FVC * 50% predicted. After the first 20 patients have randomized, patients with FVC 40% - 50% predicted will be allowed to be randomized in the
study but randomization for these patients will be capped at 20;
8. Change in FVC (measured in liters) between Screening and Day 1 (pre-dose measurement) must be a < 10% relative difference;
9. 30 * % DLCO * 90% at Screening;

10. In the investigator's opinion, no evidence of improvement in measure of IPF disease severity over the preceding year;
11. FEV1/FVC * 70%;
12. Able to understand and sign a written informed consent form;
13. 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

1. Significant clinical worsening of IPF between Screening and Day 1, in the opinion of the investigator;
2. Not a suitable candidate for enrollment or unlikely to comply with the requirements of this study, in the opinion of the investigator;
3. History of acute IPF exacerbation requiring hospitalization in the last3 months;
4. History of clinically significant environmental exposure known to cause pulmonary fibrosis, including but not limited to drugs (such as amiodarone), asbestos, beryllium, radiation, and domestic birds;
5. Known explanation for interstitial lung disease, including but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus, viral hepatitis, and cancer;
6. Clinical diagnosis of any connective tissue disease, including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis;
7. Current diagnosis of asthma or chronic obstructive pulmonary disease;
8. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis;
9. Females with a positive pregnancy test at Screening or are currently breastfeeding
10. Any history of malignancy likely to result in significant disability or likely to require significant medical or surgical intervention within the next 6 months. This does not include minor surgical procedures for localized cancer (e.g., basal cell carcinoma);
11. Any condition other than IPF that, in the opinion of the investigator, is likely to result in the death of the patient within the next 6 months;
12. History of severe hepatic impairment or end-stage liver disease or ALT or AST greater than 5 times the upper limit of normal at Screening;
13. History of end-stage renal disease requiring dialysis
14. Participation in a clinical study with administration of an investigational drug product within the previous 30 days, or five half-lives of the previously administered investigational product.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-08-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pirfenidone Solution for Inhalation
Generic name:	N/A

Ethics review

Approved WMO Date:	20-12-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	06-05-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-01-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-08-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-08-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	ACTRN12618001838202p
EudraCT	EUCTR2018-003388-75-NL
CCMO	NL68352.100.18

Study results

Date completed:	16-07-2021
Results posted:	16-08-2022

First publication
01-01-1900