Trial Description

Title

Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF) - A randomized, double-blind, placebo-controlled, parallel group, multi-center, phase II trial

Trial Acronym

RELIEF

URL of the trial

[---]*

Brief Summary in Lay Language

The aim of the study is to investigate whether treatment with pirfenidone can improve lung function in patients with progressive, non-IPF lung fibrosis. To this end, patients will be randomly assigned to treatment with pirfenidone (intervention) or placebo (control). Treatment lasts for 48 weeks. The success of each treatment will be assessed by the forced vital capacity (FVC), which is defined as the total volume expired forcefully with greatest force and speed after a maximal inspiration. Pirfenidone will be considered as effective if the FVC between start and end of treatment in the intervention group improves much more than in the control group.

Brief Summary in Scientific Language

To assess the safety and efficacy of treatment with pirfenidone compared to placebo in patients with progressive, non-IPF lung fibrosis. Patients will be randomly assigned to the control (placebo) arm and intervention arm (pirfenidone) in a 1:1 ratio. Treatment lasts for 48 weeks.

Indications for inclusion:

1. Fibrotic NSIP, 2. Chronic Hypersensitivity Pneumonitis 3. Lung fibrosis associated with collagen / vascular diseases, 4. Asbestos-induced lung fibrosis

Primary efficacy analysis and population:
Primary endpoint: Absolute change in percent predicted FVC from baseline to week 48

H0: “no difference in primary endpoint between the pirfenidone and placebo group”

H1: “difference in primary endpoint between the pirfenidone and placebo group”

The null hypothesis is tested against the alternative hypothesis at a two-sided
significance level of 5 % using a rank analysis of covariance (ANCOVA) model with a classification effect for treatment and indication and baseline FVC as a covariate. Data will be analyzed in the intent-to-treat (IIT) population.

Safety:
Safety data will be summarized using descriptive statistical methods.
Secondary endpoint(s):
Secondary outcomes will be analyzed using appropriate statistical methods.
There is one planned interim analysis for efficacy.

Amendment Nr. 3, EK Votum Az.: 473-15 fed from 01.02.2018 Exclusion criterion Nr. 19 is added.
Time for stable treatment with ph-spez. therapy is in med view of the LKP with 12 weeks adequate

Organizational Data

- DRKS-ID: **DRKS00009822**
- Date of Registration in DRKS: **2016/01/13**
- Date of Registration in Partner Registry or other Primary Registry: [---]*
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **473-15 fed , Ethik-Kommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München**

Secondary IDs

- EudraCT-No.
  (for studies acc. to Drug Law): **2014-000861-32**

Health condition or Problem studied

- ICD10: **J84.1 - Other interstitial pulmonary diseases with fibrosis**
- ICD10: **J68.4 - Chronic respiratory conditions due to chemicals, gases, fumes and vapours**

Interventions/Observational Groups

- Arm 1: **Pirfenidone Esbriet (2403 mg/d) = 9 capsules daily for 48 weeks**
- Arm 2: **Treatment with placebo**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: [---]*
Study Type: **Interventional**

Study Type Non-Interventional: [---]*

- **Allocation**: Randomized controlled trial
- **Blinding**: [---]*
- **Who is blinded**: patient/subject, investigator/therapist, caregiver, assessor, data analyst
- **Control**: Placebo
- **Purpose**: Treatment
- **Assignment**: Parallel
- **Phase**: II
- **Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels)**: No

### Primary Outcome

Absolute change in percent predicted FVC from baseline to week 48

### Secondary Outcome

Key secondary endpoints: Time to disease worsening, progression-free survival as well as selected measures of pulmonary function, quality of life questionnaires and safety parameters.

### Countries of recruitment

- DE Germany

### Locations of Recruitment

- University Medical Center, **Universitätsklinikum Gießen und Marburg GmbH, Standort Gießen Medizinische Klinik und Poliklinik II**, Gießen
- University Medical Center, **Medizinische Klinik und Poliklinik V, München-Grosshadern**
- University Medical Center, **Thoraxklinik-Heidelberg gGmbH, Heidelberg**
- Medical Center, **LungenClinic Abteilung für Pneumologie, Grosshansdorf**
- University Medical Center, **Medizinische Hochschule Klinik für Pneumologie, Hannover**
- University Medical Center, **Ruhlandklinik, Westdeutsches Lungenzentrum am Universitätsklinikum Essen gGmbH Abteilung Pneumologie-Allergologie, Essen**
- Medical Center, **Zentralklinik Bad Berka Klinik für Pneumologie, Bad Berka**
Recruitment

- Planned/Actual: Actual
- (Anticipated or Actual) Date of First Enrollment: 2016/04/05
- Target Sample Size: 374
- Monocenter/Multicenter trial: Multicenter trial
- National/International: National

Inclusion Criteria

- Gender: Both, male and female
- Minimum Age: 18 Years
- Maximum Age: 80 Years

Additional Inclusion Criteria

Confident diagnosis of progressive, non-IPF lung fibrosis due to ALF, CVDLF, chronic HP or fNSIP:
1. Clinical symptoms consistent with ALF, CVDLF, chronic HP or fNSIP, including the insidious onset of otherwise unexplained dyspnea on exertion prior to
2. Diagnosis of either ALF, CVDLF, chronic HP or fNSIP based on diagnostic criteria outlined in Table 1, at least 9 months before randomization

3. Women of childbearing capacity are required to have a negative serum pregnancy test before treatment and must agree to maintain highly effective methods of 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, then one of the two methods of birth control should be an oral contraceptive (e.g., oral contraception and a spermicide)

Table 1 Diagnostic criteria for ALF, CVDLF, chronic HP and fNSIP (patients need to fulfill all of the listed diagnostic criteria within one of the categories)

Asbestos-induced lung fibrosis
- Existence of asbestos-specific pleural changes in HRCT (pleural plaques)
- Reticular changes in HRCT and restrictive lung function pattern
- History of asbestos exposure
- Absence of an alternative explanation for fibrotic lung disease
- Absence of extensive pleural plaques and/or effusion

Lung fibrosis associated with collagen / vascular diseases
- Diagnosis of progressive systemic sclerosis (PSS), mixed connective tissue disease (MCTD), rheumatoid arthritis (RA), Sjögren’s syndrome, polymyositis/dermatomyositis on the basis of extrapulmonary symptoms and corresponding proof of auto-antibodies
- Reticular changes in HRCT and restrictive lung function pattern
- Absence of an alternative explanation for fibrotic lung disease

Chronic Hypersensitivity Pneumonitis
- Previous or current respiratory symptoms (dyspnea, coughing) with a temporal or spatial relation to a causative antigen exposure
- Proof of precipitating antibody and/or lymphocytic alveolitis (>30%)
- HRCT consistent with chronic HP
- Restrictive lung function pattern
- Absence of an alternative explanation for fibrotic lung disease

Fibrotic NSIP
- Histological diagnosis of a fibrotic NSIP pattern by open lung biopsy or cryobiopsy
- HRCT consistent with fibrotic NSIP
- Restrictive lung function pattern
- Absence of an alternative explanation for fibrotic lung disease, especially no clinical suspicion of CVD

4. 18 ≤ Age ≤ 80 years

Disease Severity and Progression:
5. Progressive disease in absence of a particular treatment (ALF) or despite a previous or concomitant treatment as outlined in protocol chapter 7.11. Progression prior to study entry must be proven by calculating the slope of a set of at least 3 previous FVC measurements within at least 6 months and at maximum 24 months before screening, showing a (eventually extrapolated) FVC decline of at least 5% (abs. pred.) per year

6. Percent predicted FVC ≥40%, but < 90% at the Screening Visit (before randomization)
7. Percent predicted, hemoglobin (Hb)-corrected carbon monoxide diffusing capacity/carbon monoxide transfer capacity (DLCO) ≥10%, but < 90% at the Screening Visit
8. Distance walked ≥150 meters, with O2 saturation >83% on ≤ 6L/min of O2

Informed Consent and Protocol Adherence:
9. Able to understand and sign a written informed consent form
10. Able to understand the importance of adherence to study treatment and the study protocol, including the concomitant medication restrictions throughout the study period

Lung transplantation:
11. Patients being considered or on the waiting list for lung transplantation are eligible for participation only if their estimated waiting time is longer than the study period. At the time these patients are placed on the list the date and reason for this placement and the LAS should be collected

Exclusion criteria

Disease-Related Exclusions:
1. Not a suitable candidate for enrolment or unlikely to comply with the requirements of this study, in the opinion of the investigator
2. May not survive the study period, in the opinion of the investigator
3. Premature withdrawal from a randomized clinical trial in the previous 2 years for any reason other than Sponsor decision or current participation in a clinical drug trial
4. Obvious additional obstructive lung disease, as evident from a) forced expiratory volume in the first second (FEV1)/FVC ratio <0.7 after administration of bronchodilator at Screening Visit, OR b) bronchodilator response defined by an increase of ≥12% and an increase of ≥ 200 mL in the FEV1 after bronchodilator use compared to the value seen before bronchodilator at the Screening Visit, OR c) residual volume (RV) >140% of predicted (before administration of bronchodilator)
5. Other explanation for interstitial lung disease, including but not limited to radiation, sarcoidosis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV), viral hepatitis and cancer
6. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis
7. In the clinical opinion of the investigator, the patient is expected to need and be eligible for a lung transplant within 52 weeks after randomization
8. Unable to undergo pulmonary function testing

Medical Exclusions:
9. Any history of malignancy likely to result in death or significant disability or likely to require significant medical or surgical intervention within the next 2 years. This does not include minor surgical procedures for localized carcinoma (e.g. basal cell carcinoma)
10. Any condition other than lung fibrosis which, in the opinion of the investigator, is likely to result in the death of the patient within the next 2 years
11. History of advanced cirrhosis or clinically significant liver disease
12. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous 6 months, including but not limited to the following:
   • Myocardial infarction, unstable angina pectoris, coronary artery bypass surgery, or coronary angioplasty
   • Congestive heart failure requiring hospitalization
   • Uncontrolled arrhythmias
   • Asthma or chronic bronchitis requiring hospitalization in the last 6 months
13. Any condition, which, in the opinion of the investigator, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone
14. Poorly controlled diabetes (defined by glycosylated hemoglobin [HbA1C] >10 %)
15. Pregnancy or lactation
16. History of alcohol or substance abuse in the past 2 years
17. History of any condition or habit associated with altered consciousness and a risk of aspiration in the past 2 years
18. Family or personal history of long QT Syndrome
19. Treatment with either one of the following medications: fluvoxamine (any time), any investigational drug, Stable treatment with PH-specific medication for less than 12 weeks. For individual cases, exemptions can be made after consultation with the Coordination Investigator (LKP) and/or the deputy Coordinating Investigator.

20. Severe pulmonary hypertension with PVR values > 900 dyn

21. Smoking

Laboratory Exclusions:

22. Any of the following liver function test criteria above specified limits: total bilirubin >2.5 upper limit of normal (ULN); aspartate or alanine aminotransferase (AST/SGOT or ALT/SGPT) >2.5 ULN; alkaline phosphatase >2.5 ULN

Concomitant Therapy Exclusions:

23. Severe liver failure


25. Hypersensitivity/allergy against pirfenidone or any component of the IMP

26. History of angioedema in relation to prior use of pirfenidone

27. Severe renal failure defined as GFR < 30ml/min and/or need for dialysis

28. Concomitant therapy with potential interaction to study drug according to SmPC

29. Patients are excluded, if more than 15 mg prednisolon equivalent are applied per day, or if a pre-existent steroid and/or immunosuppressant therapy has been modified within the last 3 months and/or if such therapy would be needed to be changed during the study period. In that case, dosing has to be adjusted and patient must be re-checked for eligibility 3 months after the last dose adjustment.

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Status

- Recruitment Status: Recruiting stopped after recruiting started
- Study Closing (LPLV): [---]*

Trial Publications, Results and other documents

* This entry means the parameter is not applicable or has not been set.
*** This entry means that data is not displayed due to insufficient data privacy clearing.