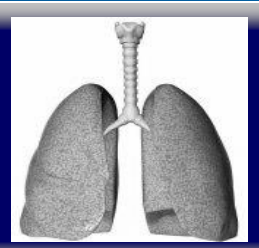
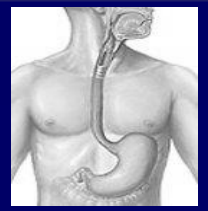
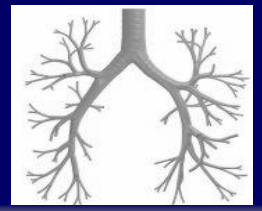
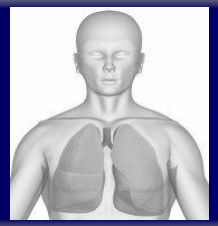


# Pulmonary Fibrosis / ILD Trials


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Steward

***Topics:***

- **Why participate in a trial**
- **How to determine what type of trial is best for you**
- **How to identify available trials**
- **What are differences between phase I, II, and III trials**
- **IPF trials**
- **Progressive fibrosing – ILD trials**
- **Specific connective tissue disease trials**
- **Pulmonary hypertension trials**
- **Clinical trial logistics**

## *Why participate in a trial*

- **New therapies can't be developed and approved without first being studied in humans**
- **Make a contribution to the larger community / pay it forward**
- **Free medical care (though care for complications gets billed to insurance/patient)**
- **Often a learning / enlightening experience**
- **Potentially gain access to a new, hopefully helpful therapy**

**Other thoughts?**

## *How to determine what type of trial is best for you*

- **First priority is to clarify your diagnosis – trials are specific to particular diagnoses**
- **Consider phase**
- **Inclusion / Exclusion criteria – PFTs data, age, duration of illness, additional medical conditions, EKG abnormalities, certain medications, others…**
- **Duration of trial, number of visits, transportation support**
- **Method of drug delivery (pill, injection, nebulization)**
- **Randomization (1:1, 2:1, etc.), open-label extension**

**Other considerations?**

## *How to identify available trials*

- **Speak with your pulmonary doc**
- **Poke around the web**
- **Researchmatch.org**
- **Pulmonary Fibrosis Foundation**
- **Clinicaltrials.gov**

## *What are differences between phase I, II, and III trials*

**<u>Phase I</u>** **usually first trial involving humans, small numbers, safety is emphasis. No placebo, efficacy explored though not focus.**

**If medication is safe:**

**<u>Phase II</u>** **first trial to explore efficacy – does the medication work? Additional safety information obtained. Larger numbers, placebo group included.**

**If medication is safe and appears to work:**

**<u>Phase III</u>** **does the medication work in larger groups of patients and/or is it better than currently used treatments. Randomized, larger numbers, longer.**

**If medication is safe and effective – FDA approval pursued**

## *IPF trials*

**Phase III Trials:**

| | | |
|---|---|---|
| **Pamrevlumab (FG-3019)** | **Fibrogen** | **CTGF mAB** |
| **PRM-151** | **Promedior/Roche** | **recombinant pentraxin-2 (PTX-2) - a.k.a. serum amyloid P** |

**Trial:** **Evaluation of Efficacy and Safety of Pamrevlumab in Patients With Idiopathic Pulmonary Fibrosis [ZEPHYRUS]**

**Medication:** **Pamrevlumab (FG-3019) 30 mg/kg IV every 3 weeks**

**Phase:** **III**

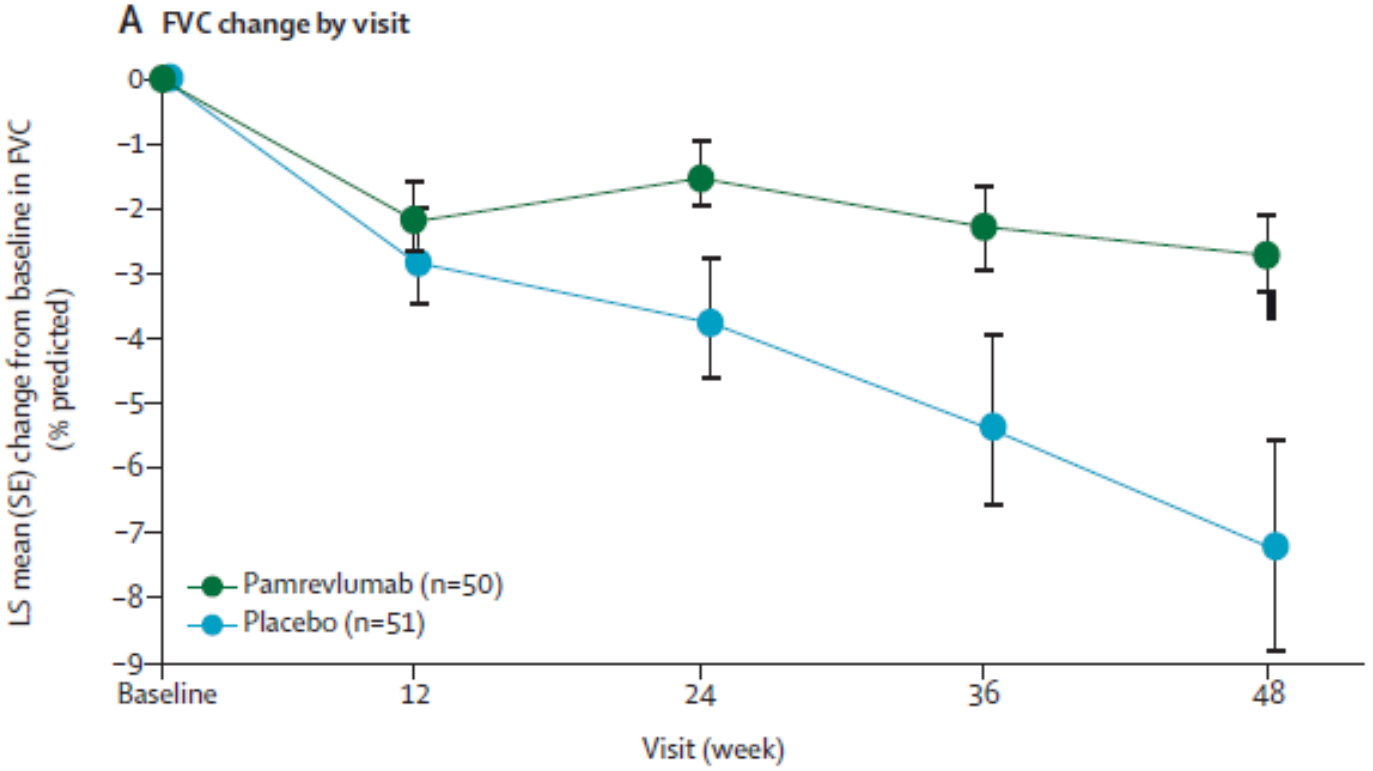
**Inclusion / exclusion criteria considerations:** **nintedanib and pirfenidone not allowed**

**Randomization:** **1:1**

**Duration:** **48 weeks**

**Open label extension:** **yes**

**Sites:** **RIH**




| | Pamrevlumab (n=50) | Placebo (n=53) |
|---|---|---|
| Any adverse event* | 48 (96%) | 52 (98%) |
| Serious adverse events | 12 (24%) | 8 (15%) |
| All reported deaths† | 3 (6%) | 6 (11%) |
| Adverse events leading to treatment or study discontinuation | 10 (20%) | 10 (19%) |
| Serious adverse events leading to treatment or study discontinuation | 3 (6%) | 7 (13%) |
| Infusion-associated adverse events | 20 (40%) | 14 (26%) |
| Most frequent adverse events‡ | | |
| Respiratory tract infection | 15 (30%) | 11 (21%) |
| Cough | 14 (28%) | 23 (43%) |
| Dyspnoea | 14 (28%) | 11 (21%) |
| Idiopathic pulmonary fibrosis | 10 (20%) | 9 (17%) |
| Fatigue | 10 (20%) | 4 (8%) |
| Urinary tract infection | 10 (20%) | 4 (8%) |
| Nasopharyngitis | 9 (18%) | 5 (9%) |
| Sinusitis | 8 (16%) | 8 (15%) |
| Diarrhoea | 8 (16%) | 4 (8%) |
| Nausea | 7 (14%) | 7 (13%) |
| Headache | 4 (8%) | 6 (11%) |
| Bronchitis | 2 (4%) | 6 (11%) |

Richeldi L et al. Lancet Respir Med 2020; 8:25-33.

**Trial:** **A Study to Evaluate the Efficacy and Safety of Recombinant Human Pentraxin-2 in Participants With Idiopathic Pulmonary Fibrosis**

**Medication:** **rhPTX-2 (PRM-151) 10 mg/kg IV on Days 1, 3 and 5 followed by infusions every 4 weeks**

**Phase:** **III**

**Inclusion / exclusion criteria considerations:** **stable dose of pirfenidone or nintedanib allowed**

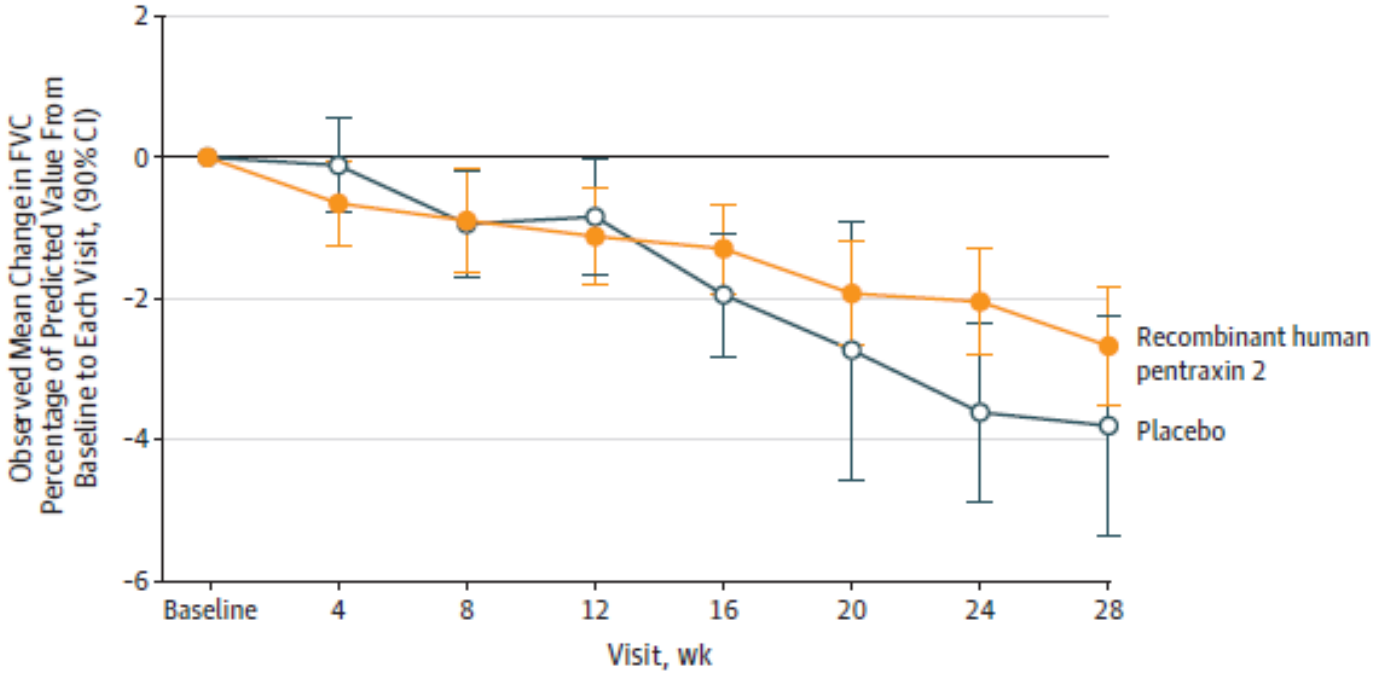
**Randomization:** **1:1**

**Duration:** **48 weeks**

**Open label extension:** **No**

**Sites:** **MGH, BIDMC**

Observed mean change in FVC percentage of predicted value from baseline to each visit, all patients




| Events | No. (%) of Patients With Event | |
|---|---|---|
| | Recombinant Human Pentraxin 2 (n = 77) | Placebo (n = 39) |
| Any adverse event | 71 (92) | 36 (92) |
| Most frequent adverse events[b] | | |
| Cough | 14 (18) | 2 (5) |
| Fatigue | 13 (17) | 4 (10) |
| Nasopharyngitis | 12 (16) | 9 (23) |
| Headache | 11 (14) | 3 (8) |
| Idiopathic pulmonary fibrosis | 11 (14) | 5 (13) |
| Diarrhea | 9 (12) | 2 (5) |
| Bronchitis | 8 (10) | 5 (13) |
| Dyspnea | 7 (9) | 4 (10) |
| Upper respiratory tract infection | 7 (9) | 5 (13) |
| Back pain | 3 (4) | 4 (10) |
| Severe adverse events[c] | 7 (9) | 2 (5) |
| Serious adverse events[d] | 6 (8) | 4 (10) |
| Fatal adverse events | 0 | 1 (3) |
| Adverse events leading to discontinuation | 2 (3) | 1 (3) |
| Pneumonia | 0 | 1 (3) |
| Lung carcinoma cell type unspecified stage II | 1 (1) | 0 |
| Idiopathic pulmonary fibrosis | 1 (1) | 0 |

Raghu G et al. JAMA. 2018;319(22):2299-2307

# Phase II Trials (incomplete list)

| | | |
|---|---|---|
| BMS-986278 | BMS | LPA1 receptor antagonist |
| TD139 | Galecto Biotech | inhaled galectin-3 inhibitor |
| setanaxib (GKT137831) | Selleck | NOX1/NOX4 inhibitor |
| GLPG1205 | Galapagos | GPR84 inhibitor |
| Ianalumab (VAY736) | Novartis | mAb anti-B-cell activating factor (BAFF) receptor |
| belumosudil (KD025) | Kadmon Corporation | Rho-associated coiled-coil kinase 2 (ROCK2) inhibitor |
| PLN-74809 | Pliant Therapeutics | αvβ6/αvβ1 inhibitor |
| ND-L02-s0201 | Nitto Denko Corporation / BMS | HSP47 siRNA |
| saracatinib | AstraZeneka | Src tyrosine kinase inhibitor |
| CC-90001 | Celgene | Mitogen-activated protein kinase 8 inhibitor |

**Trial:** **A Study Measuring the Effectiveness, Safety, and Tolerability of BMS-986278 in Participants With Lung Fibrosis**

**Medication:** **BMS-986278 30 mg or 60 mg twice daily**

**Phase:** **II**

**Inclusion / exclusion criteria considerations:** **stable dose of pirfenidone or nintedanib allowed; IPF and other types of pulmonary fibrosis included**

**Randomization:** **1:1:1**

**Duration:** **26 weeks**

**Open label extension:** **yes**

**Sites:** **St. E's**

**Trial:** **Evaluation of Efficacy and Safety of PLN-74809 in Patients With Idiopathic Pulmonary Fibrosis**

**Medication:** **PLN-74809, variable doses, oral**

**Phase:** **II**

**Inclusion / exclusion criteria considerations:** **stable dose of pirfenidone or nintedanib allowed**

**Randomization:** **1:1**

**Duration:** **26 weeks**

**Open label extension:** **no**

**Sites:** **MGH**

**Trial:** **JUNIPER: A Phase 2 Study to Evaluate the Safety, Biological Activity, and PK of ND-L02-s0201 in Subjects With IPF**

**Medication:** **ND-L02-s0201 IV every 2 weeks**

**Phase:** **II**

**Inclusion / exclusion criteria considerations:** **stable dose of pirfenidone or nintedanib allowed**

**Randomization:** **1:1:1**

**Duration:** **24 weeks**

**Open label extension:** **no**

**Sites:** **MGH**

# Progressive fibrosing – ILD trials

**PF-ILD defined as worsening pulmonary fibrosis that isn't considered IPF**

**Important to sort out whether change in immunosuppressive regimen vs. addition of anti-fibrotic makes sense**

**Can include a wide range of exposures-related fibrosis, underlying illnesses, idiopathic syndromes**

**Both nintedanib and pirfenidone have proven efficacy**

**BMS study allows PF-ILD patients though certain auto-immune conditions (a.k.a. connective tissue diseases) are excluded**

# Specific connective tissue disease trials

**RA  (RA-ILD patients allowed in BMS trial)**

**Scleroderma (systemic sclerosis)**

**Dermatomyositis**

**Trial:** Phase ll Study of Pirfenidone in Patients With RA-ILD (TRAIL1)

**Medication:** Pirfenidone 801 mg three times daily

**Phase:** II

**Inclusion / exclusion criteria considerations:** unclear if nintedanib allowed

**Randomization:** 1:1

**Duration:** 52 weeks

**Open label extension:** no

**Sites:** BWH

**Pulmonary hypertension due to interstitial lung disease / pulmonary fibrosis**

**Recently completed and published trial**

**No ongoing trials but good options for those with advanced disease**

## Existing Anti-fibrotics

**LONG overdue, most relevant ongoing trial:**

## Management of Progressive Disease in Idiopathic Pulmonary Fibrosis

**Goal**:
Evaluate the efficacy and tolerance of combined pirfenidone and nintedanib as compared to a "switch monotherapy“ in patients with worsening IPF despite receiving either pirfenidone or nintedanib

**Eligibility**:
- Stable dose of pirfenidone or nintedanib prescribed as first-line therapy for at least 6 months
- Worsening of respiratory symptoms AND ≥10% relative decline in FVC % predicted
- Worsening of respiratory symptoms AND ≥5 - <10% relative decline in FVC % predicted AND with increasing extent of fibrotic changes on chest imaging

**Intervention** – 24 weeks of:
- pirfenidone 2403 mg per day in combination with nintedanib 300 mg per day
- switch from one monotherapy to alternative

Estimated Enrollment : 210 participants
Will likely complete study in 2023

**Primary Outcome Measure** : Slope of the decline in FVC

# Clinical Trials

Arthur Dea
Steward St. Elizabeth's Medical Center
ILD Collaborative

# Clinical Trials

- Clinical research help scientists and doctors learn new information to improve medical practice and patient care.
- In a clinical trial, human volunteers (often referred to as study participants/subjects) receive specific interventions according to the research protocol.
- Clinical trials provide the basis for the development and marketing of new drugs, biological products, and medical devices.
- Clinical trials may compare the investigational medical approach to a standard one that is already available or to a placebo that contains no active ingredient.

# Who Conducts Clinical Trials?

- Every clinical trial is led by a principal investigator who is often a medical doctor. Clinical trials also have a research team that may include doctors, nurses, study coordinators, and other health care professionals.
- Clinical trials can be sponsored, or funded, by pharmaceutical companies, academic medical centers, in addition to Federal agencies such as the National Institutes of Health, the U.S. Department of Defense, and the U.S. Department of Veterans Affairs.

# Participating in Clinical Research

- A clinical study is conducted according to a research plan known as the protocol. The protocol is designed to answer specific research questions and safeguard the health of participants. It contains the following information:
  - The reason for conducting the study
  - Who may participate in the study (the eligibility criteria)
  - The number of participants needed
  - The schedule of tests, procedures, or drugs and their dosages
  - The length of study participation
  - What information will be gathered about the subjects

# How Are Participants Protected?

- Informed consent is a process used by researchers to provide potential and enrolled participants with information about a clinical study.
- This information helps people decide whether they want to enroll or continue to participate in the study.
- The informed consent process is intended to protect participants and should provide enough information for a person to understand the risks of, potential benefits of, and alternatives to the study.
- Participants may withdraw from a study at any time for any reason.

# Institutional Review Board

- Each federally supported or conducted clinical study and each study of a drug, biological product, or medical device regulated by FDA must be reviewed, approved, and monitored by an institutional review board (IRB).
- An IRB is made up of doctors, researchers, and members of the community.
- Its role is to make sure that the study is ethical and that the rights and welfare of participants are protected.
- The IRB also reviews the informed consent document.
- In addition to being monitored by an IRB, some clinical studies are also monitored data safety and monitoring boards.

# Considerations for Participation

- Participating in a clinical study contributes to medical knowledge.
- The results of these studies can make a difference in the care of future patients by providing information about the benefits and risks of therapeutic, preventative, or diagnostic products or interventions.
- The safety and the effectiveness of the experimental approach or use may not be fully known at the time of the trial.
- Some trials involve some potential risk of harm or injury to the participant, although it may not be greater than the risks related to routine medical care or disease progression. (For trials approved by IRBs, the IRB has decided that the risks of participation have been minimized and are reasonable in relation to anticipated benefits.)

# Questions to Ask Before Participating

- A potential participant should discuss the research study with his or her caregiver/family members, the research team conducting the study, and usual health care providers.
- The following questions may be helpful during such a discussion. Answers to some of these questions are provided in the informed consent document.
  - What is being studied?
  - Has the investigational medication been tested before in humans?
  - What are my chances of receiving investigational medication or placebo?
  - How often will I have to visit the hospital or clinic?
  - Will I be reimbursed for travel for compensated for my time?

# What Is ClinicalTrials.gov?

- ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions.
- The Web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH).

To learn more about clinical research participation:

- https://clinicaltrials.gov/ct2/about-studies/learn
- https://www.hhs.gov/ohrp/education-and-outreach/about-research-participation

| Procedures | Study Visits | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Screening | Day 1/ Randomization | Week 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 26/ EOS |
| Informed Consent | X | | | | | | | | |
| Physical Exam | X | X | X | X | X | X | X | X | X |
| Urine Pregnancy Test | X | | | | | | | | |
| Height and Weight Measurement | X | X | | | | X | | | X |
| ECG Measurement | X | X | | X | | X | | | X |
| Vital Signs | X | X | X | X | X | X | X | X | X |
| Clinical laboratory tests | X | X | X | X | X | X | X | X | X |
| Lung Function Tests | X | X | | X | X | X | X | X | X |
| 6-minute Walk Test | X | | | | | X | | | X |
| Questionnaires | X | | | | | X | | | X |
| High-Resolution Computed Tomography (HRCT) | X | | | | | | | | X |
| Investigational Study Medication/Placebo | | X | X | X | X | X | X | X | |
| Subject Diary | | X | X | X | X | X | X | X | |