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PILOT™

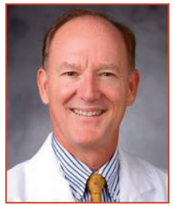
Pulmonary Fibrosis Identification:
Lessons for Optimizing Treatment

CONNECT

AUGUST 2014

IN THIS ISSUE

Dear Colleagues



The PILOT program began exactly a decade ago as the very first randomized and placebo controlled trials in IPF emerged. The hope at that time was that the trials would demonstrate safe and effective treatments for patients with IPF. The program focused on educating clinicians on the diagnosis of IPF with hope that we would have new treatment options. We organized an outstanding multidisciplinary group of expert clinicians and the result was a state-of-the art educational program that substantially raised awareness about IPF. Unfortunately, most of that decade failed to yield effective new treatments for IPF. However, persistence and novel approaches have now yielded exciting new phase III clinical trial data that will have 2014 remembered as a watershed year in IPF drug development. The results of the ASCEND trial evaluating pirfenidone and the INPULSIS trials evaluating nintedanib will likely change the future of IPF patient care. Now more than ever, the early and accurate diagnosis of IPF is of paramount importance.

I would like to invite you participate in this new PILOT endeavor. The expert panel has evolved over the decade and a superb team has been assembled to enhance your educational experience. More offerings can be accessed on **www.PILOTforIPF.org**, and I invite you to look for future editions of PILOTConnect.

Welcome to the new era in IPF!

Paul W. Noble, MD
Vera and Paul Guerin Family Distinguished Chair in Pulmonary Medicine
Professor and Chair
Department of Medicine
Director, Women's Guild Lung Institute
Cedars-Sinai Medical Center

Event Calendar

PILOT is a global initiative designed to provide comprehensive continuing medical education supporting the diagnosis and management of patients with idiopathic pulmonary fibrosis. In the coming year, the PILOT curriculum is expected to reach over 30,000 clinicians through various online and live educational activities including regional symposium, grand round and chapter meeting support, and expanded **PILOTforIPF.org** content.

Upcoming Events:

Friday, November 7
Regional Summit (Yale School of Medicine)
Navigating the New Era of IPF: Collaborative Patient Care
Register >

Wednesday, November 12
Hawaii ATS Chapter Lecture

Saturday, November 15
Regional Summit (Vanderbilt University Medical Center)
Navigating the New Era of IPF: Collaborative Patient Care
Register >

Interested in hosting a live meeting? The PILOT faculty will bring expertise in IPF diagnosis and treatment to your Grand Round series, State Chapter Meeting, or other local event. Request a live meeting in your area now!
Request a Meeting >

ASCEND Trial

ASCEND was a randomized, double-blind, placebo controlled, phase 3 study of the efficacy and safety of pirfenidone in patients with IPF.

Subjects: 555 patients with mild-to-moderate IPF

Treatment: Oral pirfenidone (801 mg) or placebo 3 times daily

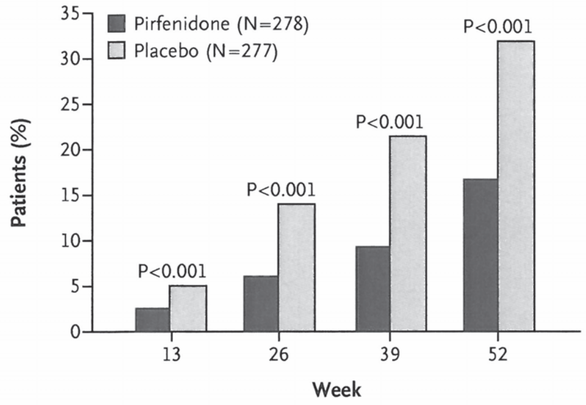
Duration: 52 weeks

Primary end point: Change in FVC or death at week 52 (met)

Secondary end points
- 6-minute walk distance (met)
- Progression-free survival (met)
- Dyspnea (not met)
- Death from any cause or from IPF (not met)

ClinicalTrials.gov identifier: NCT01366209

Figure 1. Time course of patients experiencing decreased FVC or death in ASCEND for pirfenidone and placebo treatment groups



King TE, et al. *N Engl J Med.* 2014;370(22):2083-2092.

ASCEND Trial

"[ASCEND] hit its primary endpoint...there was a 48% relative risk reduction in that endpoint [change in FVC or death]."
David Lederer, MD, MS

ASCEND Summary
- Treatment with pirfenidone for 52 weeks significantly reduced disease progression, as measured by
  - Changes in % predicted FVC ($P < 0.001$)
  - Changes in 6-minute walk distance ($P = 0.04$)
  - Progression-free survival ($P < 0.001$)
- Treatment with pirfenidone reduced all-cause mortality and treatment emergent IPF-related mortality in pooled analyses at week 52
- Treatment was generally safe, had an acceptable side effect profile, and was associated with fewer deaths.

INPULSIS Trials

INPULSIS-1 and INPULSIS-2 were randomized, double-blind, placebo-controlled, phase 3 studies of the efficacy and safety of nintedanib (BIBF 1120) in patients with IPF.

Subjects: A total of 1066 patients with mild-to-moderate IPF

Treatment: oral nintedanib (150 mg) or placebo twice daily (randomized in a 3:2 ratio)

Duration: 52 weeks

Primary end point: annual rate of decline in FVC (both trials met end point)

Secondary end points

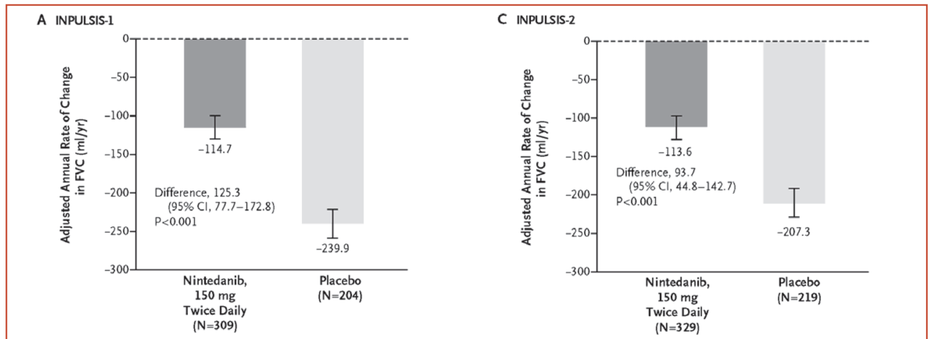
- Time to the first acute exacerbation (INPULSIS-1 did not meet, INPULSIS-2 met)
- Change from baseline in the total score on the St. George's Respiratory Questionnaire (INPULSIS-1 did not meet, INPULSIS-2 met)

ClinicalTrials.gov identifier: NCT01335464, NCT01335477

"In both trials, nintedanib showed a reduction of 50% in the FVC annual rate of decline."
Luca Richeldi, MD, PhD

INPULSIS Trials

Figure 2. Annual rate of decline in FVC in INPULSIS-1 and INPULSIS-2 for nintedanib and placebo treatment groups



Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

INPULSIS Summary

- Nintedanib had significant benefit in adjusted annual rate of change in FVC, which is consistent with a slowing of disease progression
  - INPULSIS-1: difference = 125.3 ml, $P < 0.001$
  - INPULSIS-2: difference = 93.7 ml, $P < 0.001$
- Nintedanib had significant benefit in time to the first acute exacerbation in INPULSIS-2
  - INPULSIS-1: HR = 1.15, $P = 0.67$
  - INPULSIS-2: HR = 0.38, $P = 0.005$
- Nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients

PANTHER Trial

PANTHER evaluated the effectiveness of the antioxidant N-acetylcysteine (NAC) at preventing the loss of lung function in people with IPF in a phase 3, placebo-controlled, double-blind, randomized study.

Subjects: 264 patients with mild-to-moderate IPF (2 arm continuation of PANTHER-IPF)

Treatment: N-acetylcysteine (600 mg) or placebo 3 times daily

Duration: 60 weeks

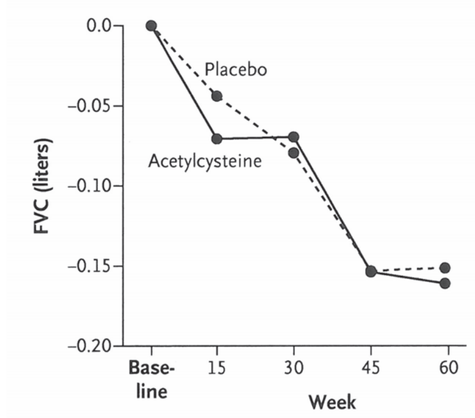
Primary end point: change in FVC (not met)

Secondary end points

- Rate of acute exacerbation (not met)
- Change from baseline in the total score on the St. George's Respiratory Questionnaire (not met)

ClinicalTrials.gov identifier:
NCT00650091

Figure 3. Time course of change from baseline in FVC for NAC and placebo treatment groups



Martinez FJ, et al. *N Engl J Med.* 2014;370(22):2093-2101.

PANTHER Trial

PANTHER Summary

- PANTHER 2012: Increased risks of death and hospitalization were observed in patients with IPF who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo
- Compelling evidence against the use of the triple combination for patients with mild-to-moderate IPF
- PANTHER 2014: NAC offered no significant benefit with respect to the preservation of FVC in patients with IPF with mild-to-moderate impairment in lung function

"The PANTHER trial shows no benefit of high dose acetylcysteine in the treatment of mild to moderate IPF."
Harold R. Collard, MD

Trial Results Review

Two of the three recent IPF phase 3 clinical trials achieved statistically significant positive results for their primary endpoints. The results reported are encouraging for patients with mild-to-moderate IPF and underscore the importance of accurate and early diagnosis. Use of pirfenidone and nintedanib in patients with more advanced disease and the role of combination therapy have not been investigated. Both pirfenidone and nintedanib have been granted Breakthrough Therapy Designation by the FDA and approval of either of these therapies will signify a watershed for patients with IPF.

Polling Questions

1. Confidence

	Low			Medium			High
What is your level of confidence in diagnosing patients with IPF?	1	2	3	4	5	6	7
What is your level of confidence in managing patients with IPF?	1	2	3	4	5	6	7

2. Two new therapies for IPF may be approved by the FDA in 2015. As new treatments become available, what will be your strategy for managing newly diagnosed patients?

a. I will refer them to an ILD Center or another specialist
b. I will consider one of the new treatments
c. I will consider one of the new treatments upon failure of my usual approach
d. I will consider a new treatment after more clinical information is available
e. N/A. I do not treat patients with IPF

3. Would you prescribe a new medication for patients with IPF even if they fell outside the inclusion criteria of the clinical studies?

a. Yes
b. Maybe
c. No

4. What is your specialty?

a. Primary care
b. Pulmonology
c. Surgery
d. Radiology
e. Pathology
f. Intensivist
g. Other (please specify) _____

5. What is your degree/certification?

a. Physician
b. Physician Assistant
c. Nurse
d. Advanced Practice Nurse
e. Pharmacist
f. Respiratory Therapist
g. Other (please specify)_____

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