# IPF Treatment: from clinical trials to daily practice

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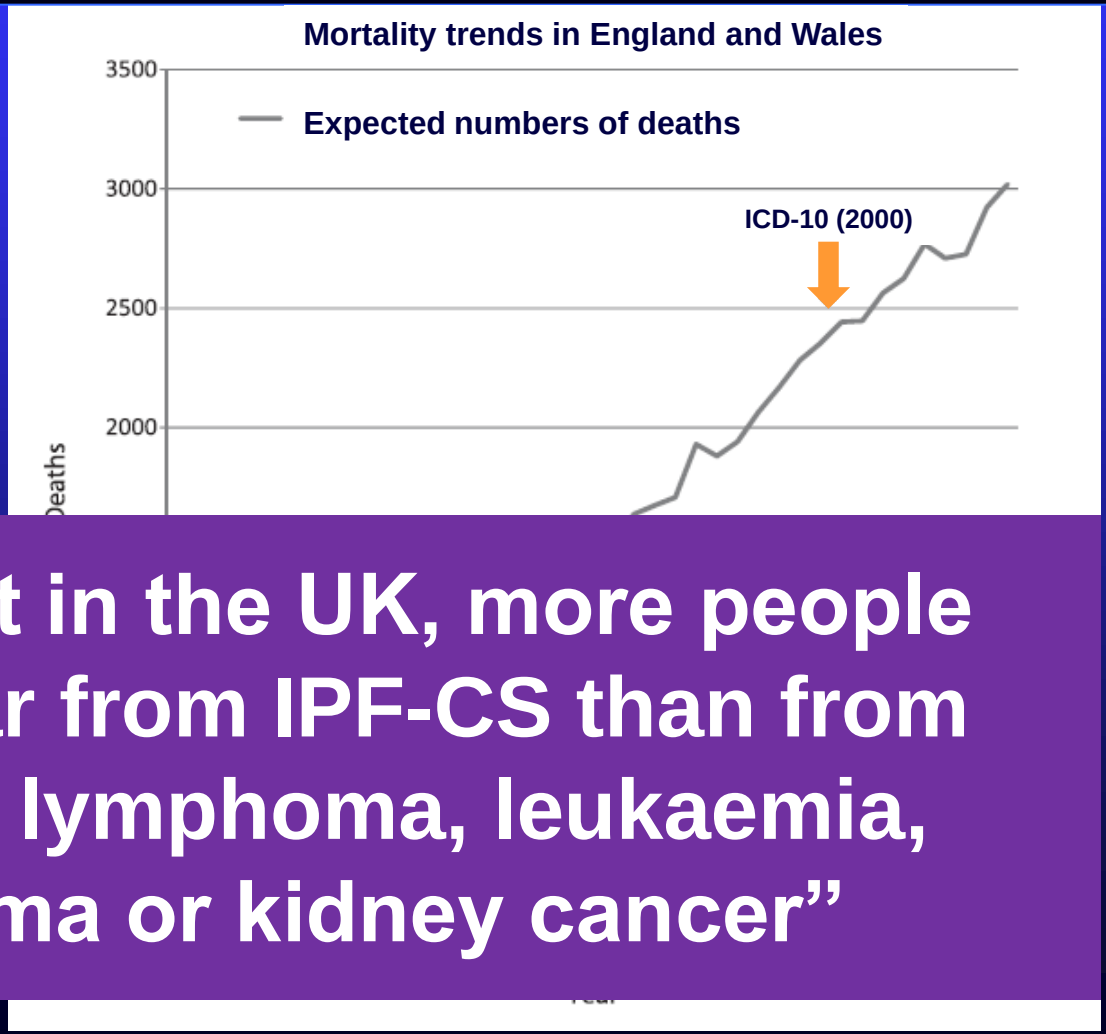
# The rising incidence of idiopathic pulmonary fibrosis in UK

Navaratnam V et al. Thorax 2011;66:462

- 15.000 people in the UK have a diagnosis of IPF-CS
- each year, 5.000 new cases of IPF




**“This means that in the UK, more people will die each year from IPF-CS than from ovarian cancer, lymphoma, leukaemia, mesothelioma or kidney cancer”**

The prevalence of IPF in Europe is ~ 120.000 and an estimated 40.000 new cases are diagnosed each year

The prevalence of IPF in Lombardy region in 2010 is 3.600 patients and incidence is 450/y

In Lombardy, IPF prevalence increased while incidence remained stable in the last years (2005-2010)

# *Rationale for New Therapeutic Approaches*

Recognition of the extremely poor prognosis of IPF

Need for prospective, randomized, controlled studies

Shift in focus from inflammation to epithelial cells and myofibroblasts

Increased understanding of disease pathogenesis points to targeted therapies

# Recent RCTs That Were Negative

- INF-gamma
- Bosentan, ambrisentan, macitentan (ERA)
- Imatinib
- Etanercept
- Sildenafil
- Warfarin

# *Treatment of idiopathic pulmonary fibrosis with ambrisentan A parallel, randomized trial*

*Raghu G. et al. Ann Inter Med 2013;158: 641 - 649*

**Objective**: To determine whether ambrisentan, an ETA receptor– selective antagonist, reduces the rate of IPF progression

**Design:** Randomized, double-blind, placebo-controlled, event driven trial (ClinicalTrials.gov: NCT00768300)

**Participants:** Patients with IPF aged 40 to 80 years with minimal or no honeycombing on HRCT

**Intervention:** Ambrisentan, 10 mg/d, or placebo

**Measurements:** Time to disease progression, defined as death, respiratory hospitalization, or a categorical decrease in lung function.

**Conclusion:** Ambrisentan was not effective in treating IPF and may be associated with an increased risk for disease progression and respiratory hospitalizations

# MUSIC Trial

| | |
|---|---|
| Full study name | Macitentan Use in an IPF Clinical Study (Phase II) |
| Agents evaluated | 10 mg, once daily |
| Projected enrollment (n) | 178 |
| Target population | Mild-to- Moderate Disease (limited HC on HRCT ≤5%) |
| Primary endpoint | FVC |

Clinical trials identifier: NCT00903331

# Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial

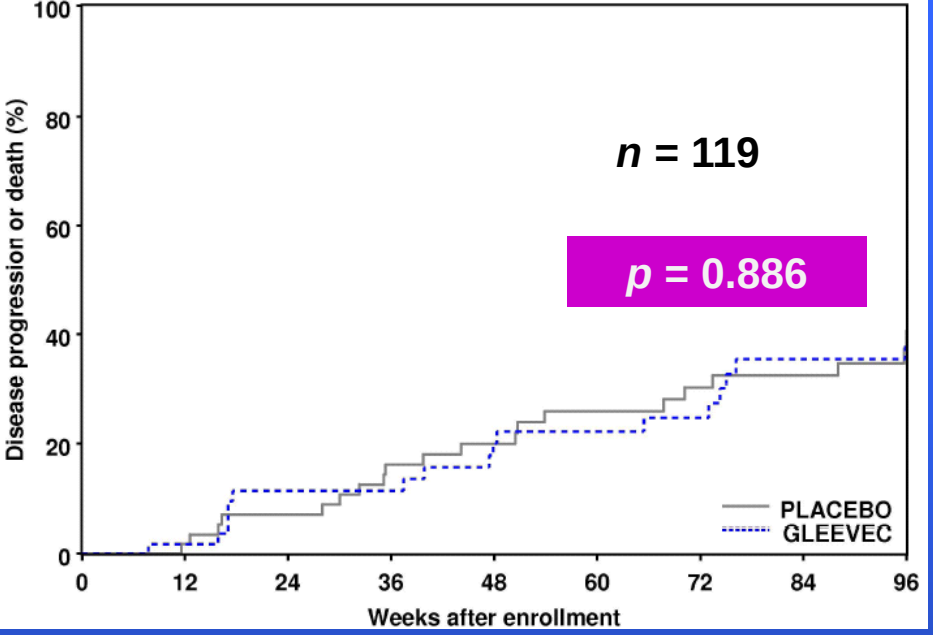
*Eur Respir J 2013; 42: 1622*

This prospective, randomised, double-blind, multicentre, parallel-group, placebo-controlled phase II trial (NCT00903331) investigated the efficacy and safety of the endothelin receptor antagonist macitentan in IPF

The primary objective was to demonstrate that macitentan (10 mg once daily) positively affected FVC versus placebo

Using a centralised system, 178 subjects were randomised (2:1) to macitentan (n=119) or placebo (n=59).

In conclusion, the primary objective was not met. Long-term exposure to macitentan was well tolerated with a similar, low incidence of elevated hepatic aminotransferases in each treatment group

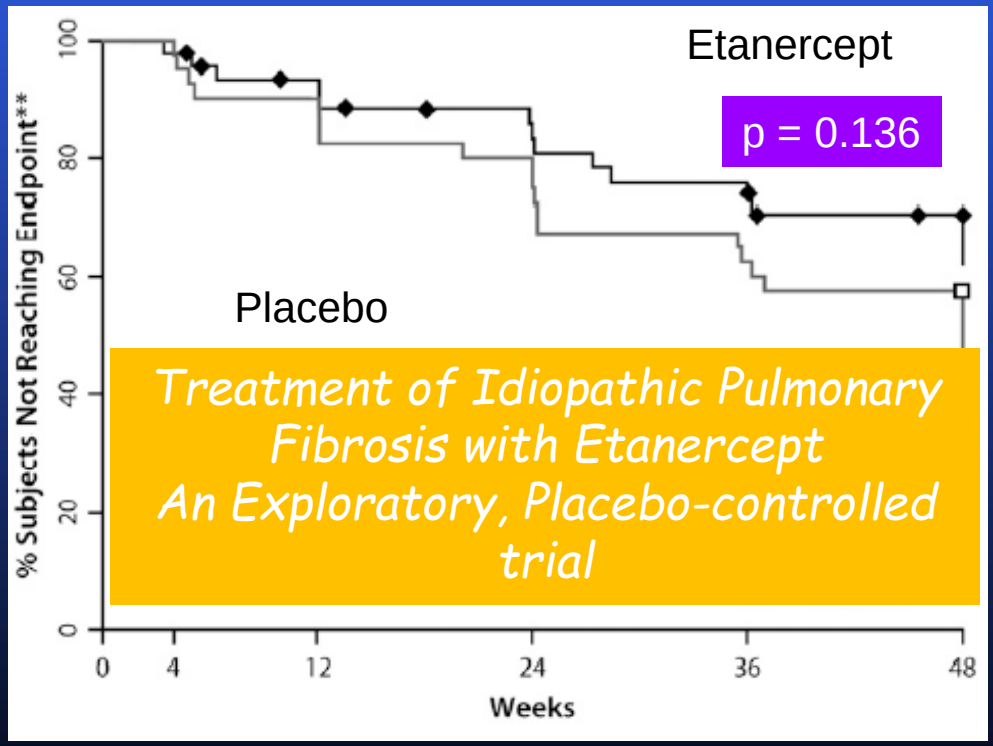



Imatinib did not significantly differ from placebo on the primary endpoint of time to disease progression

## *Imatinib clinical trial*

Daniels C, *et al. Am J Respir Crit Care Med* 2010; 181: 604-10

- The TNF-a blocking agent, etanercept, was well tolerated
- There were no differences in the predefined endpoints among patients who received etanercept or placebo




*Treatment of Idiopathic Pulmonary Fibrosis with Etanercept An Exploratory, Placebo-controlled trial*

*Am J Respir Crit Care Med 178: 948-55, 2008*

18 May 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

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# A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

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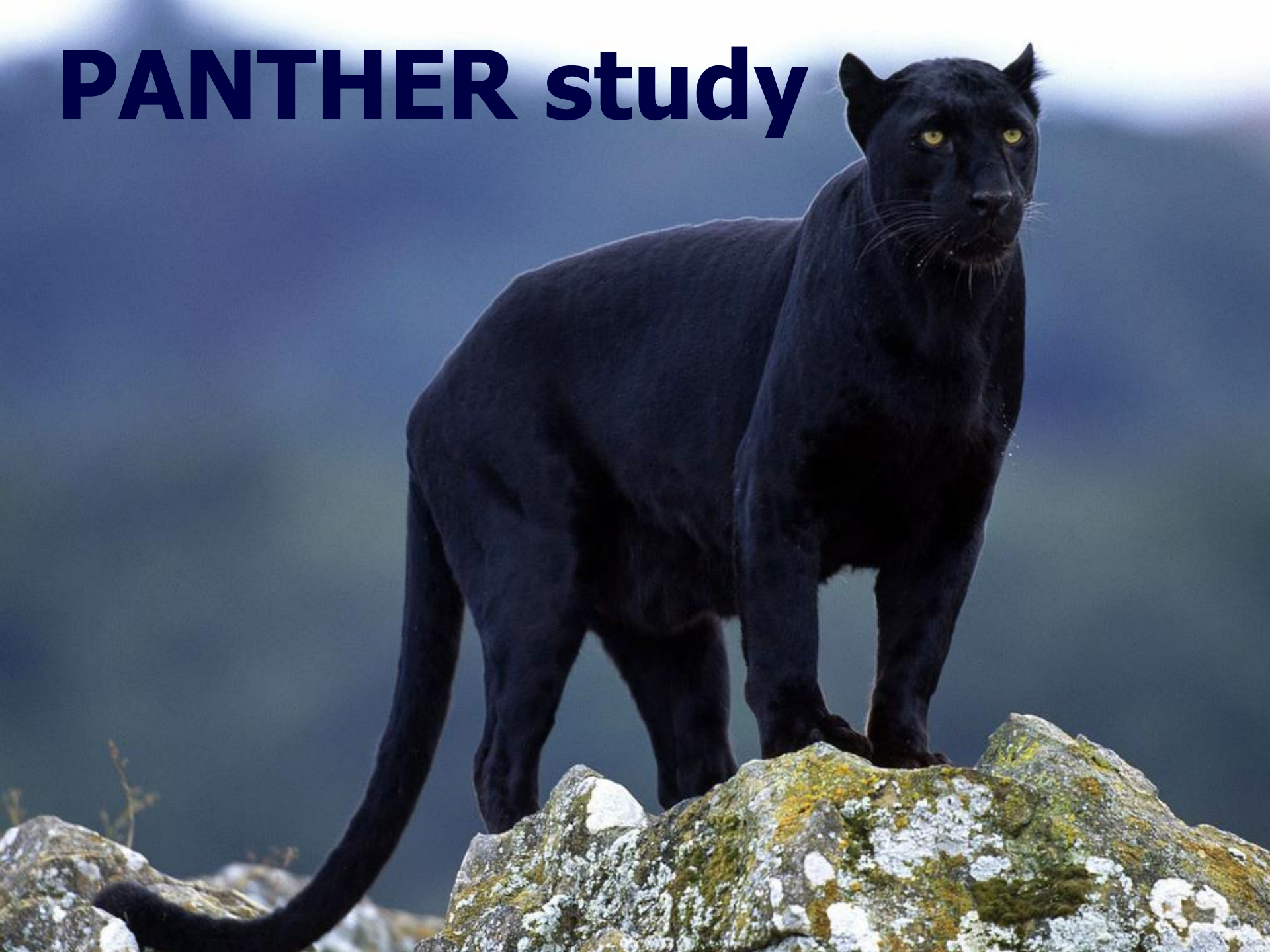
ORIGINAL ARTICLE

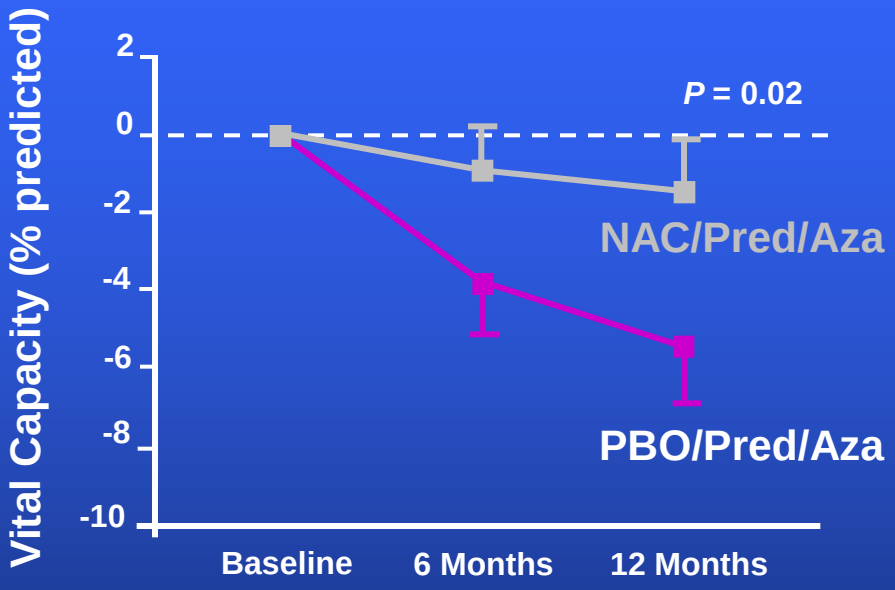
# Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

# PANTHER study

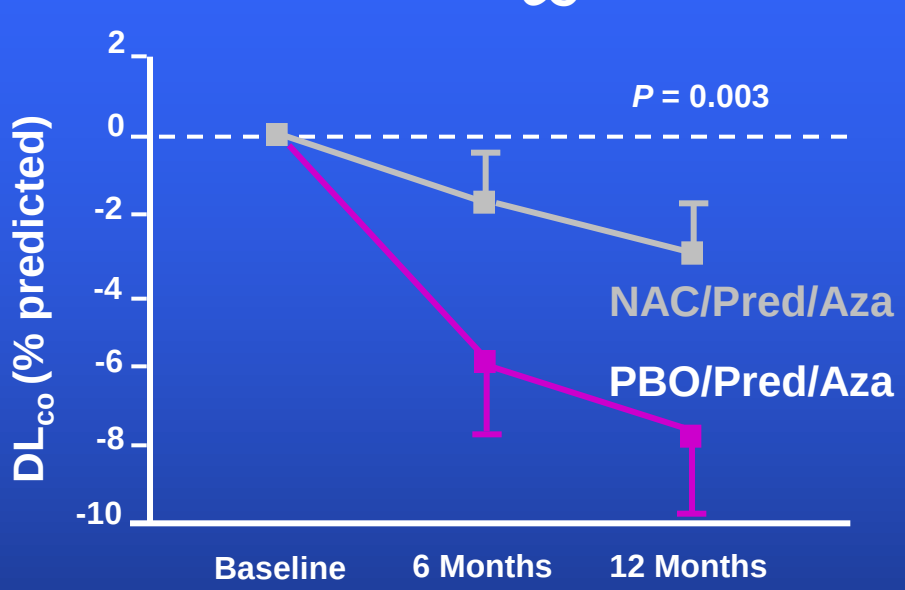


# IFIGENIA Study Results

## FVC




## $DL_{CO}$




| No. of Patients | | | | | | |
|---|---|---|---|---|---|---|
| NAC/Pred/Aza | 80 | 63 | 55 | 79 | 58 | 55 |
| PBO/Pred/Aza | 75 | 60 | 51 | 74 | 59 | 51 |

| | Mortality, *P* = NS |
|---|---|
| NAC/Pred/Aza | 7/80 (9%) |
| Placebo/Pred/Aza | 8/75 (11%) |

No mortality difference

Demedts M, et al. *N Engl J Med.* 2005;353:2229-2242

# Prednisone/Azathioprine/NAC PANTHER Trial

| | |
|---|---|
| Classification | Combination therapy |
| Mechanisms | Antiinflammatory, immunosuppression, antioxidant |
| Trial Design | Randomized, double blind, placebo controlled |
| Inclusion Criteria | FVC > 50% and $DL_{CO}$ > 30% |
| Primary Endpoint | Change in FVC % predicted |
| Treatment Arms | Placebo vs Pred/Aza/NAC vs NAC |
| Number of Patients | 236 |
| Treatment Duration | 52 weeks |
| Result | Ongoing |

# *Press Release, 21 october 2011*

Commonly used three-drug regimen for idiopathic pulmonary fibrosis found harmful

NIH stops one treatment arm of trial; other two treatments to continue

The interim results from this study showed that compared to placebo, those assigned to triple therapy had greater mortality (11 percent versus 1 percent), more hospitalizations (29 percent versus 8 percent), and more serious adverse events (31 percent versus 9 percent) and also had no difference in lung function test changes. Participants randomly assigned to the triple- therapy arm also remained on their assigned treatment at a much lower rate (78 percent adherence versus 98 percent adherence).

# Prednisone, Azathioprine and N-Acetylcysteine for pulmonary fibrosis

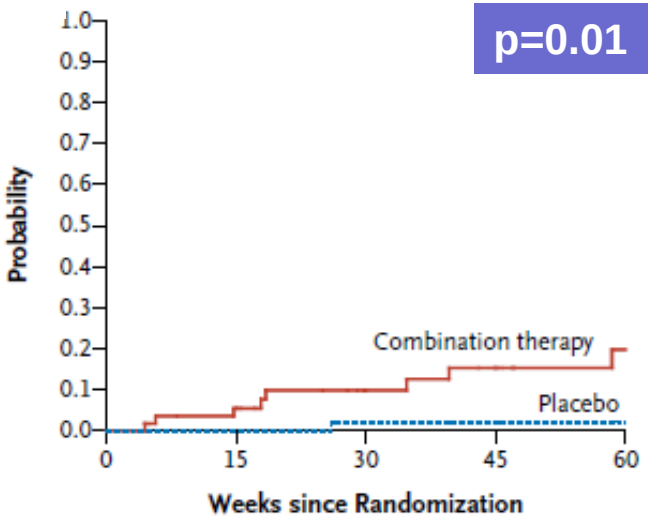
The Idiopathic Pulmonary Fibrosis Clinical Research Network

N Eng J Med 2012

**Safety end point**

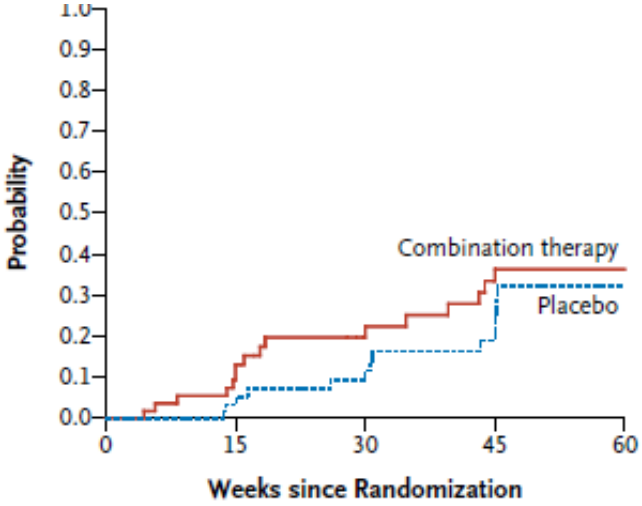
| End point | Combination therapy (n= 77) | Placebo (n= 78) | P value |
|---|---|---|---|
| Death – no. (%) | | | |
| From any cause | 8(10) | 1 (1) | 0.01 |
| From respiratory cause | 7(9) | 1 (1) | 0.02 |
| Hospitalization for any cause – no.(%) | 23 (30) | 7 (9) | <0.001 |
| Acute exacerbation – no. (%) | 5 (6) | | 0.03 |
| Serious adverse events - no. (%) | 24 (31) | 8 (10) | 0.001 |

## Time to death




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Combination therapy | 77 | 50 | 34 | 29 | 14 |
| Placebo | 78 | 57 | 44 | 31 | 17 |

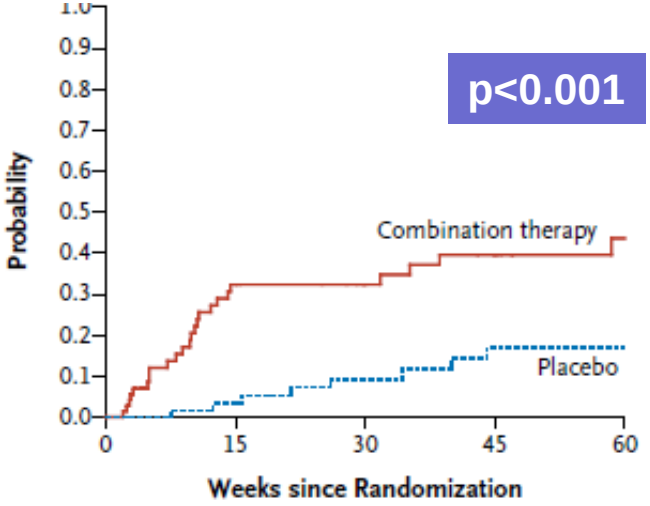
## Time to death or disease progression




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Combination therapy | 77 | 46 | 29 | 22 | 12 |
| Placebo | 78 | 55 | 39 | 24 | 11 |

These findings provide evidence against the use of this combination in IPF patients

## Time to death or hospitalization




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Combination therapy | 77 | 40 | 29 | 23 | 10 |
| Placebo | 78 | 55 | 42 | 26 | 16 |

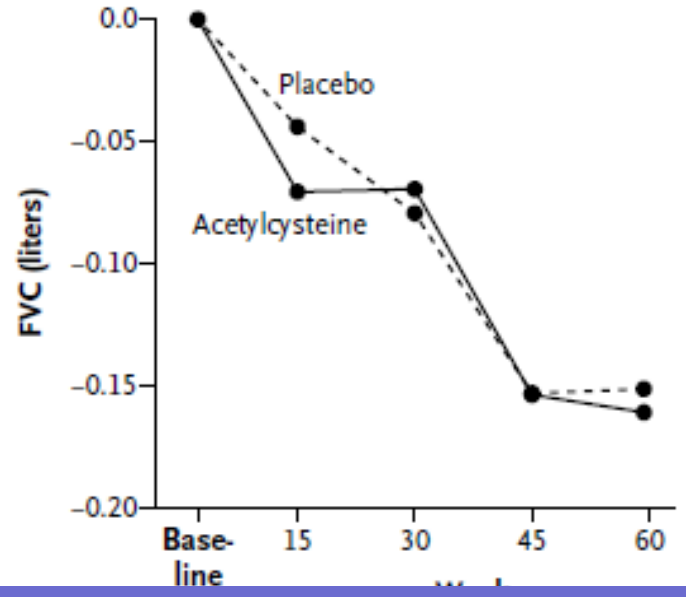
N Eng J Med 2012

# *Randomized Trial of Acetylcisteine in Idiopathic Pulmonary fibrosis*

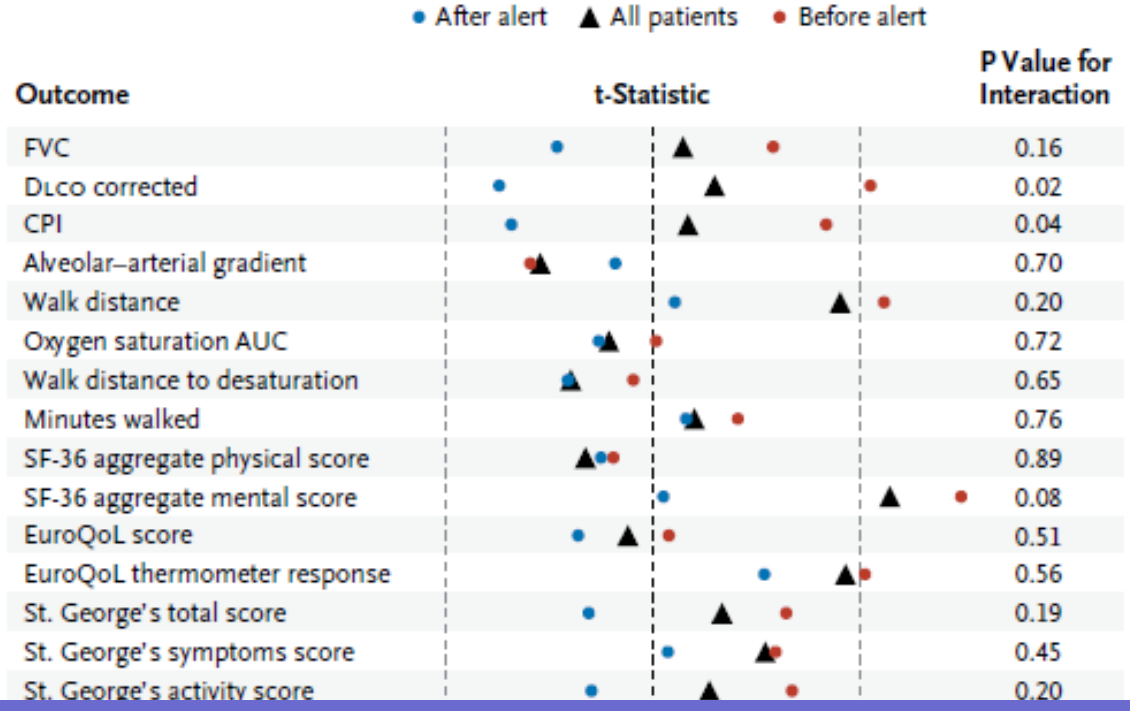
*The Idiopathic Pulmonary Fibrosis Clinical Research Network*

N Eng J Med 2014

**A Change from Baseline in FVC**



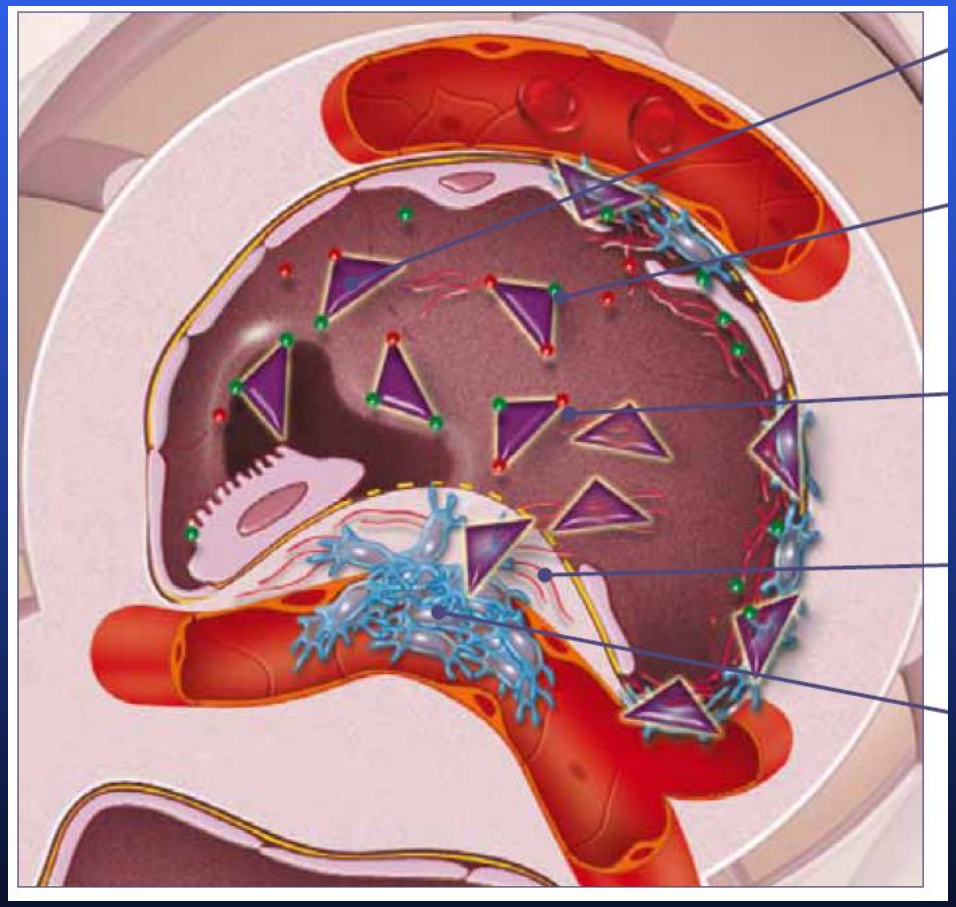

**B**




**Conclusion**: As compared with placebo, acetylcysteine offered no significant benefit with respect to the preservation of FVC in patients with IPF with mild to-moderate impairment in lung function

# Pirfenidone anti-fibrotic activity

- Orally available, synthetic molecule that exhibits anti-fibrotic properties in a variety of in vitro studies and in vivo models



Pirfenidone

Pirfenidone inhibits TGF-β, a potent mediator of lung fibrosis

Pirfenidone inhibits TNF-α synthesis, another fibrotic mediator and inflammatory cytochine

Pirfenidone inhibits collagen production

Pirfenidones attenuates fibroblast proliferation

# *Pirfenidone approved as first treatment for mild-to-moderate IPF in the EU*

- Approved by the European Commission on February 28th 2011 and currently available in many european countries
- Indicated in mild-to-moderate IPF patients – these were characterized in the pivotal Phase 3 studies by the following functional criteria:
  - FVC ≥ 50% of predicted
  - DLCO ≥ 35% of predicted
  - 6MWT distance ≥ 150 m

# Pirfenidone double-blind placebo-controlled studies in IPF

| Study (geographic location) | Regimen | Phase | Patients Randomized (n) | |
|---|---|---|---|---|
| Study 004 (Europe/US/Australia) | Pirfenidone 2403 mg/day* vs placebo vs pirfenidone1197 mg/day | 3 | 435 | Analyses of pooled data were pre-specified to derive precise estimates of magnitude of treatment effect† |
| Study 006 (Europe/US/Australia) | Pirfenidone 2403 mg/day* vs placebo | 3 | 344 | |
| SP2 (Japan) | Pirfenidone 1800 mg/day vs placebo | 2 | 109 | |
| SP3 (Japan) | Pirfenidone 1800 mg/day vs placebo | 3 | 275 | |

*The pirfenidone 2403 mg/day dose in the EU/USA/Australia studies was determined by applying the weight-adjusted 1800 mg/day dose used in the Shionogi Phase 2 (SP2) study to the expected trial population.
†but remain exploratory due to 006 not reaching the primary endpoint.

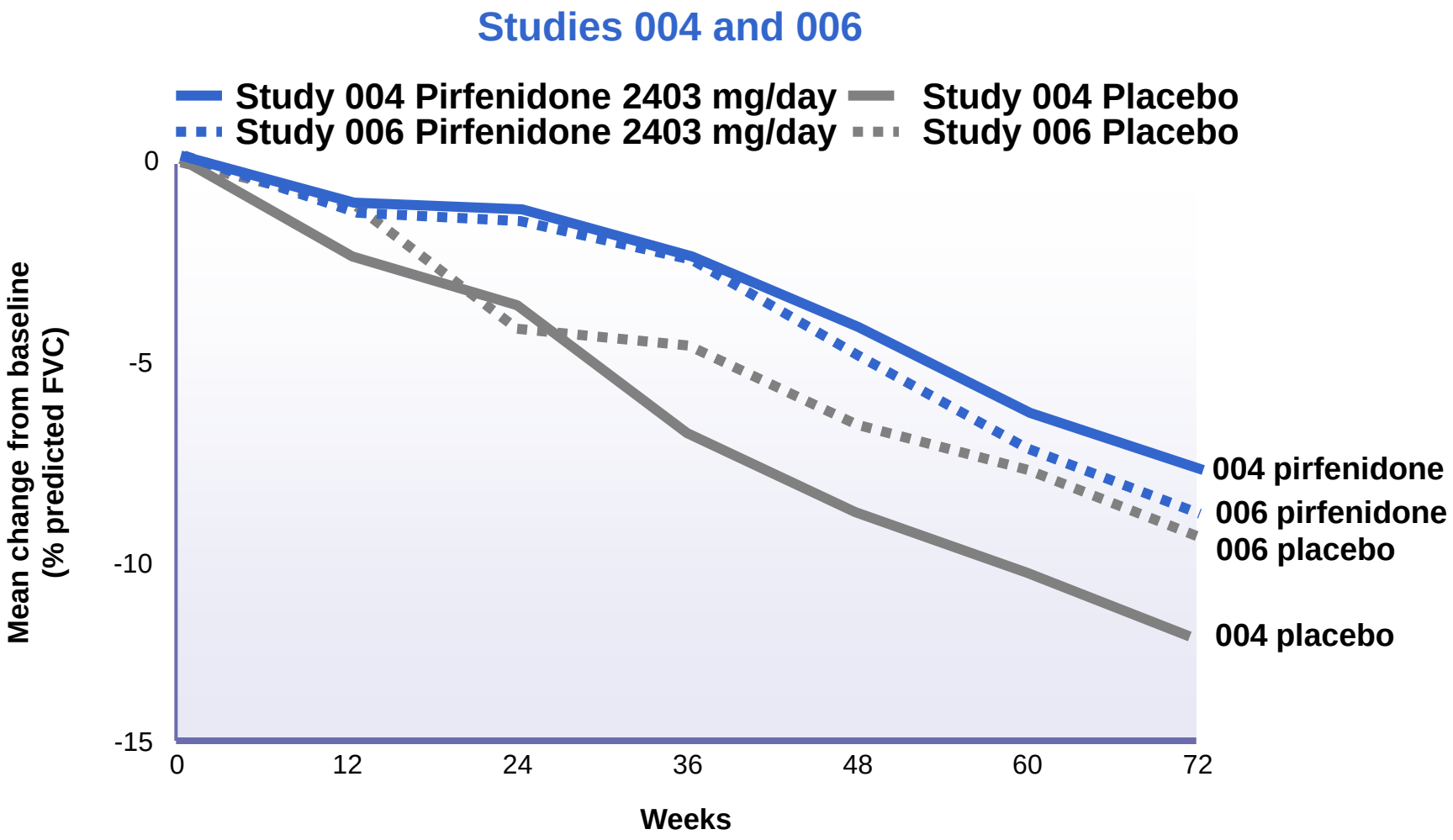
Azuma A, Nukiwa T, Tsuboi E, et al. Am J Respir Crit Care Med 2005;171:1040–1047. Taniguchi H, Ebina M, Kondoh Y, et al. Eur Respir J 2010;35:821–829. Noble PW, Albera C, Bradford WZ, et al. Lancet 2011;377:1760-1769.

# Pirfenidone
# CAPACITY 1 e 2 Trials

| | |
|---|---|
| Classification | TGFβ inhibitor |
| Mechanism | Antifibrotic |
| Trial Design | Randomized, double blind, placebo controlled |
| Inclusion Criteria | Age 40–80 years, confident IPF diagnosis<br>FVC ≥ 50% predicted value, $DL_{CO}$ ≥ 35% predicted value |
| Efficacy Endpoints | Primary: Mean change from baseline in % predicted FVC<br>Secondary: Changes in symptoms, functional capacity, QOL |
| Treatment Arms | CAPACITY 1: PFD 2403 mg/d vs placebo<br>CAPACITY 2: PFD 1197 mg/d vs PFD 2403 mg/d vs placebo |
| Number of Patients | CAPACITY 1: 344<br>CAPACITY 2: 435 |
| Treatment Duration | 72 weeks |

**King TE, *et al. AJRCCM* 2011**

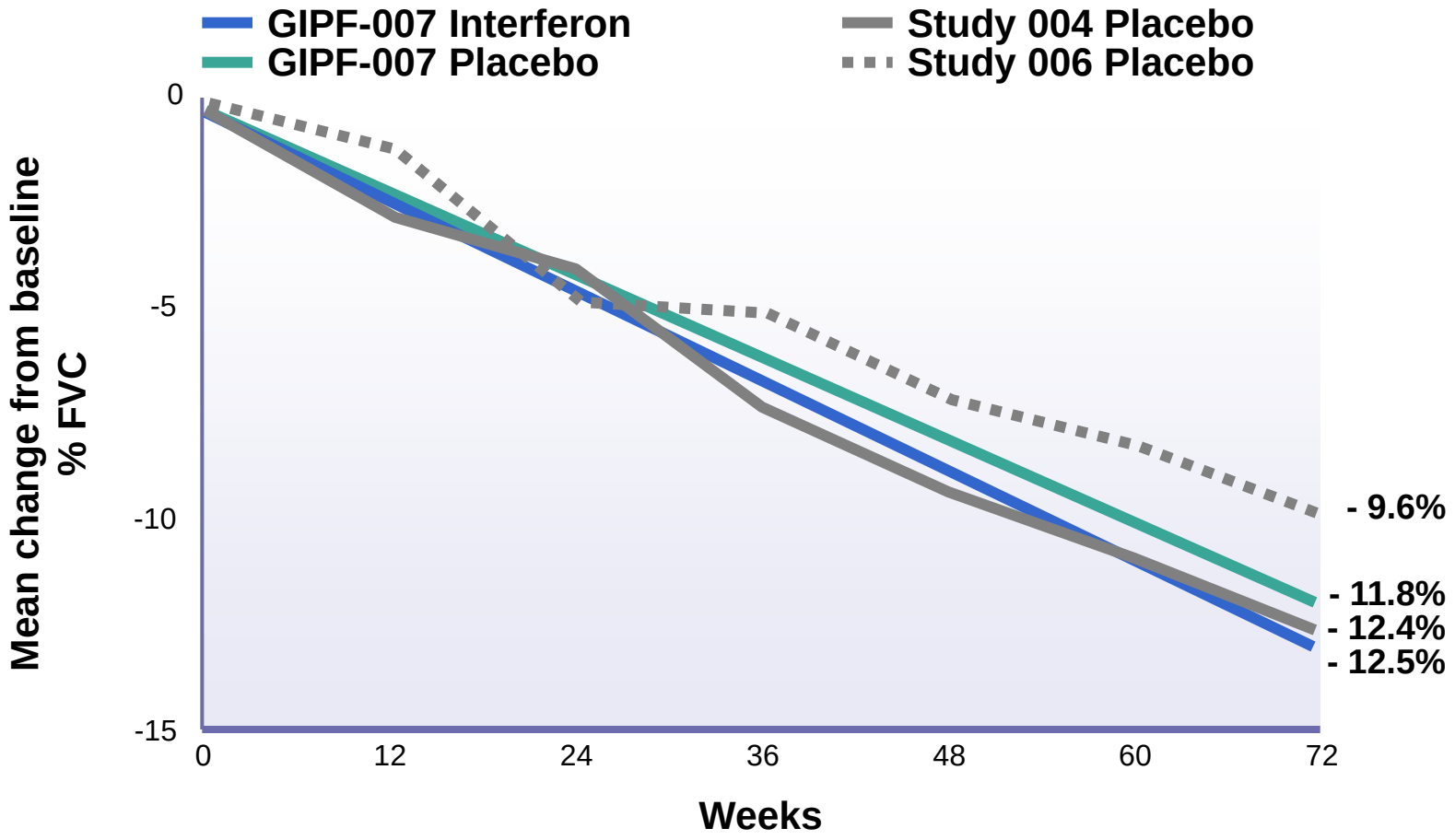
# Percent Predicted FVC Over Time




P<0.001 for Study 004 (CAPACITY 2); P=0.503 for Study 006 (CAPACITY 1)

# Change in % Predicted FVC Over Time

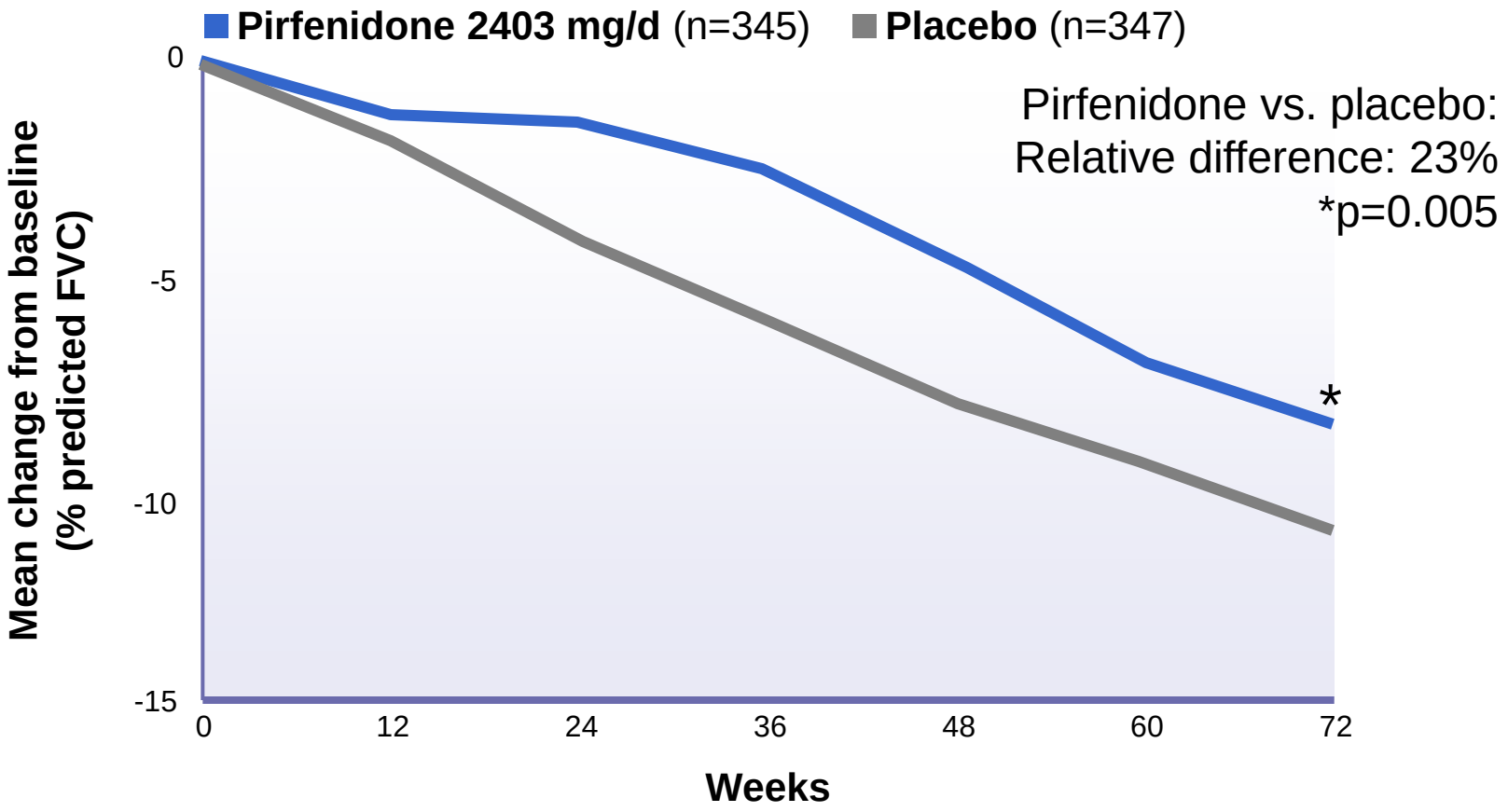
## Studies 004 (CAPACITY 2) and 006 (CAPACITY 1) Placebo vs. INSPIRE (GIPF-007)




- % predicted FVC decline in the placebo group in Study 006 (CAPACITY 1) was less than in Study 004 (CAPACITY 2) or the GIPF-007 study

# Percent Predicted FVC Over Time

**Pooled analysis of Studies 004 (CAPACITY 2) and 006 (CAPACITY 1)**




Noble PW, Albera C, Bradford WZ, et al. Lancet. 2011;377:1760-1769.

# Meta-analysis of pirfenidone treament effect

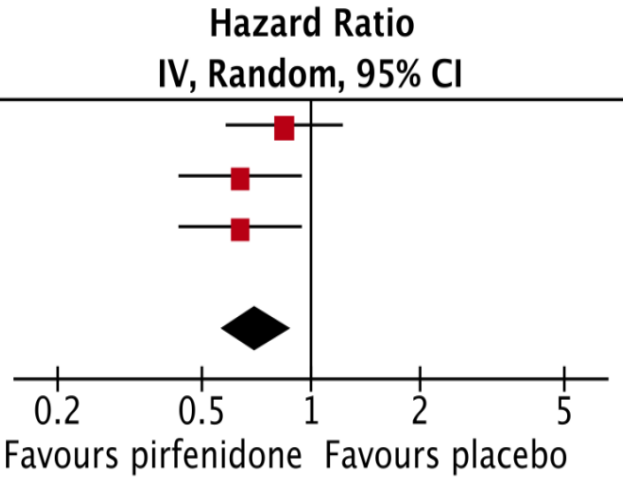
**Event driven analysis of either 10% decline in FVC or all cause mortality**

(Progression Free Survival)

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Capacity 1 | -0.17 | 0.19 | 35.7% | 0.84 [0.58, 1.22] |
| Capacity 2 | -0.45 | 0.2 | 32.2% | 0.64 [0.43, 0.94] |
| Taniguchi 2010 | -0.45 | 0.2 | 32.2% | 0.64 [0.43, 0.94] |
| **Total (95% CI)** | | | **100.0%** | **0.70 [0.56, 0.88]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.40$, df = 2 (P = 0.50); $I^2 = 0\%$

Test for overall effect: Z = 3.09 (P = 0.002)




Based in part on unpublished data

**N= 997 patients**



Spagnolo P, Del Giovane C, Luppi F, et al. Cochrane Database Syst Rev 2010;9:CD003134.

# Results Summary

- CAPACITY 1 (PIPF-006) did not achieve statistical significance on its primary endpoint, but did provide supportive evidence of a favorable treatment effect of pirfenidone
- CAPACITY 2 (PIPF-004) demonstrated a statistically significant treatment effect on the primary endpoint and key secondary endpoints
- Pirfenidone was safe and generally well-tolerated
- Excellent study conduct enabled delivery of high quality data

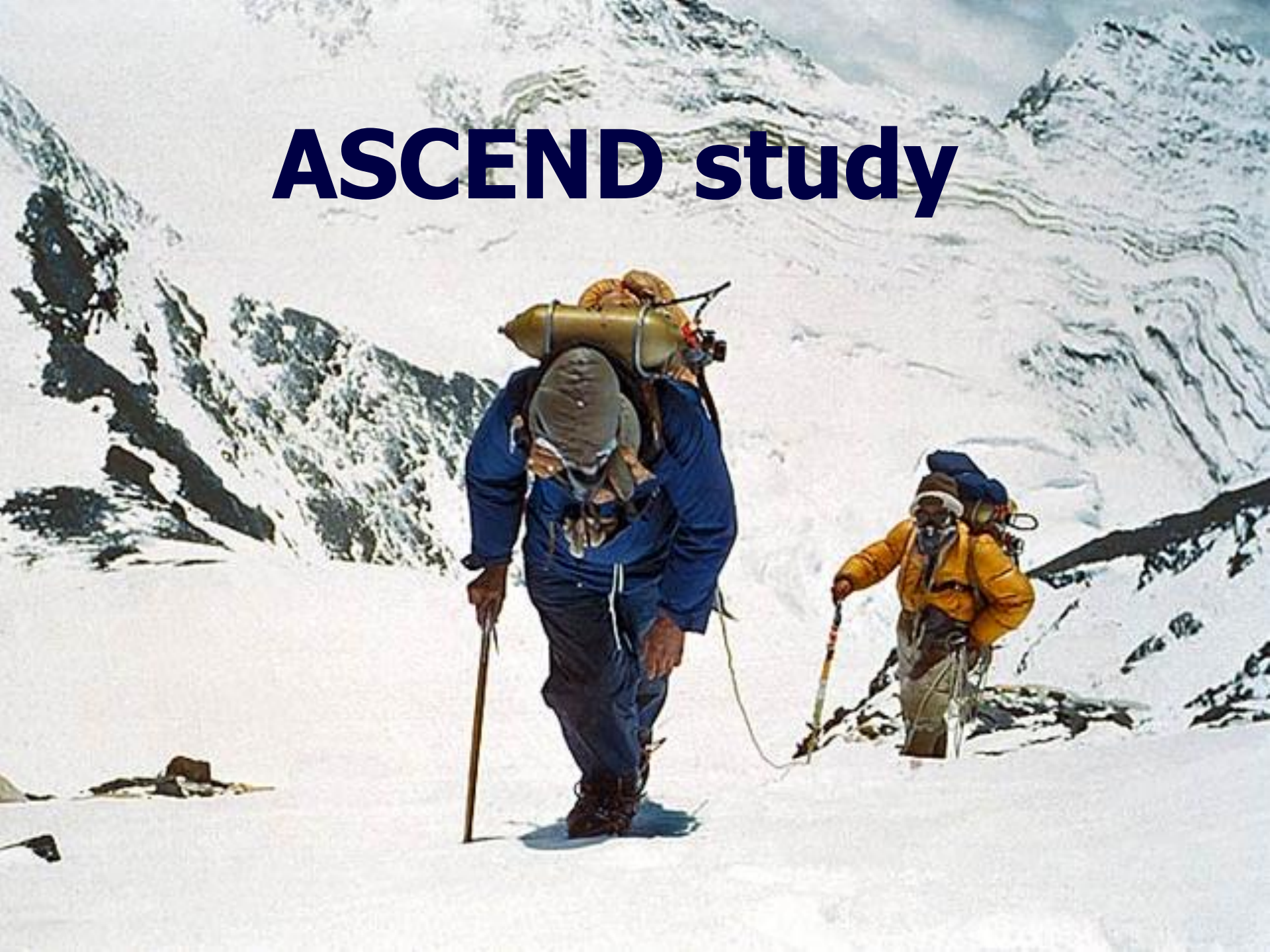
# Action on Pirfenidone for IPF

## U.S.A. FDA decision

- **NOT** approved for IPF
- Expert panel recommended approval (9-3)
- FDA comments
  - Perform a 3rd IPF pirfenidone trial of same duration as CAPACITY
    - Δ FVC as primary endpoint is acceptable
    - Improvement in patient survival will be important for drug approval

# InterMune Initiates Phase 3 ASCEND Study of Pirfenidone in IPF

# ASCEND study



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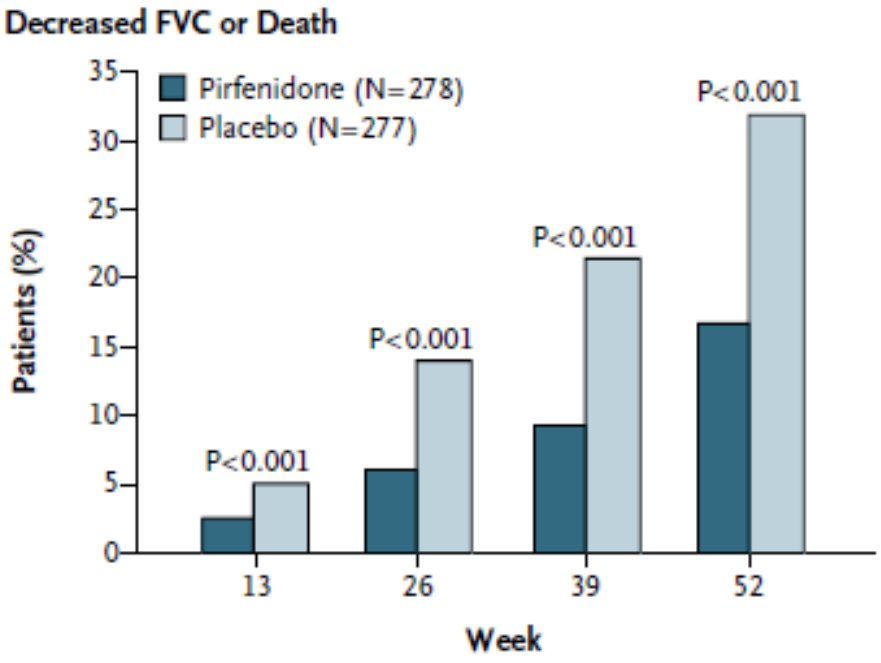
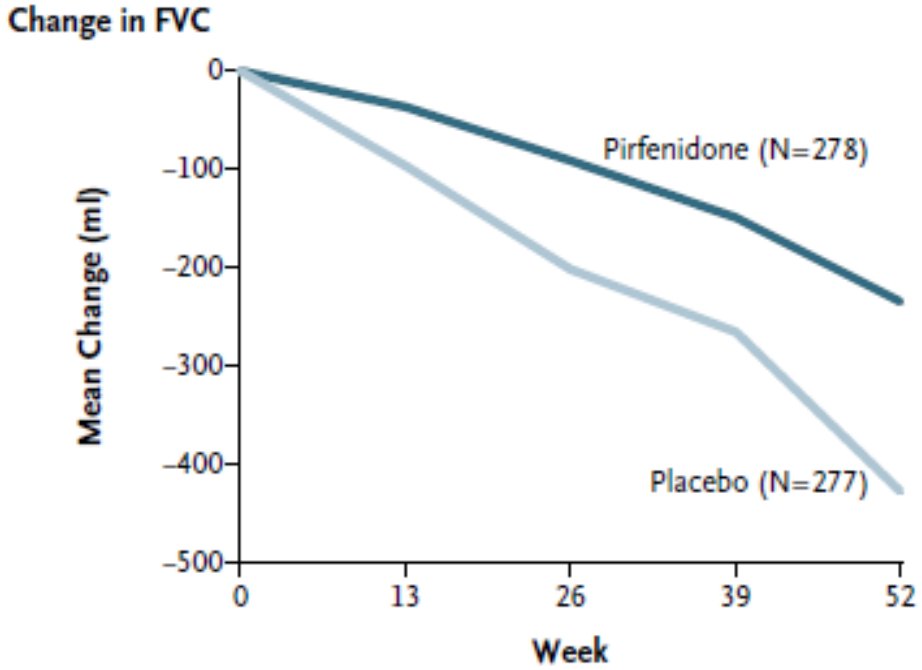
ORIGINAL ARTICLE

# A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis



# ASCEND Study Design
## *Eligibility*

- Age: 40–80 years
- HRCT: Confident diagnosis of IPF
  - Definite UIP, or
  - Possible UIP, with confirmation on SLB
- FVC: ≥50% and ≤90% percent of predicted
- $DL_{CO}$: ≥30% and ≤90% percent of predicted
- $FEV_1$/FVC ratio: ≥0.80
- Centralized review: spirometry, HRCT, SLB, deaths

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# ASCEND Study Design
## Primary Endpoint

- Percent of predicted FVC change from baseline to week 52
  - **Primary analysis:** Rank ANCOVA to test for differences in the distribution between groups
  - **Magnitude of effect**: Categorical analysis of 2 clinically important thresholds of change:
    - ≥10% decline in %FVC or death,
    - No %FVC decline

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

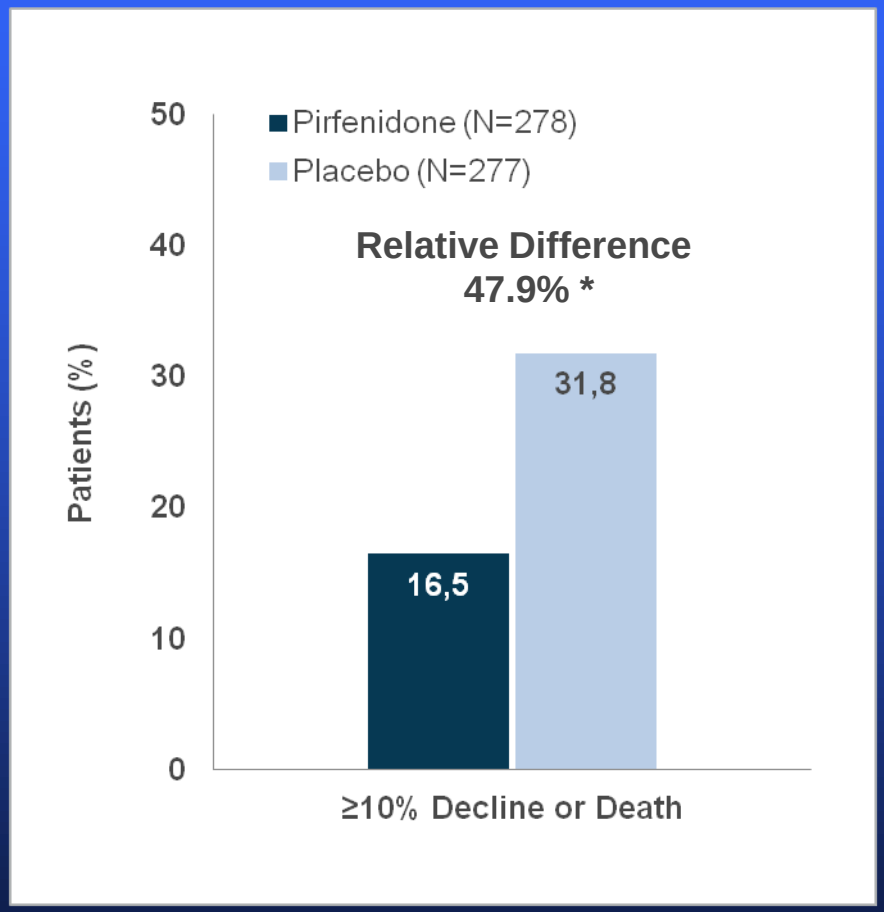
# ASCEND Study Design
## Key Secondary Efficacy Endpoints

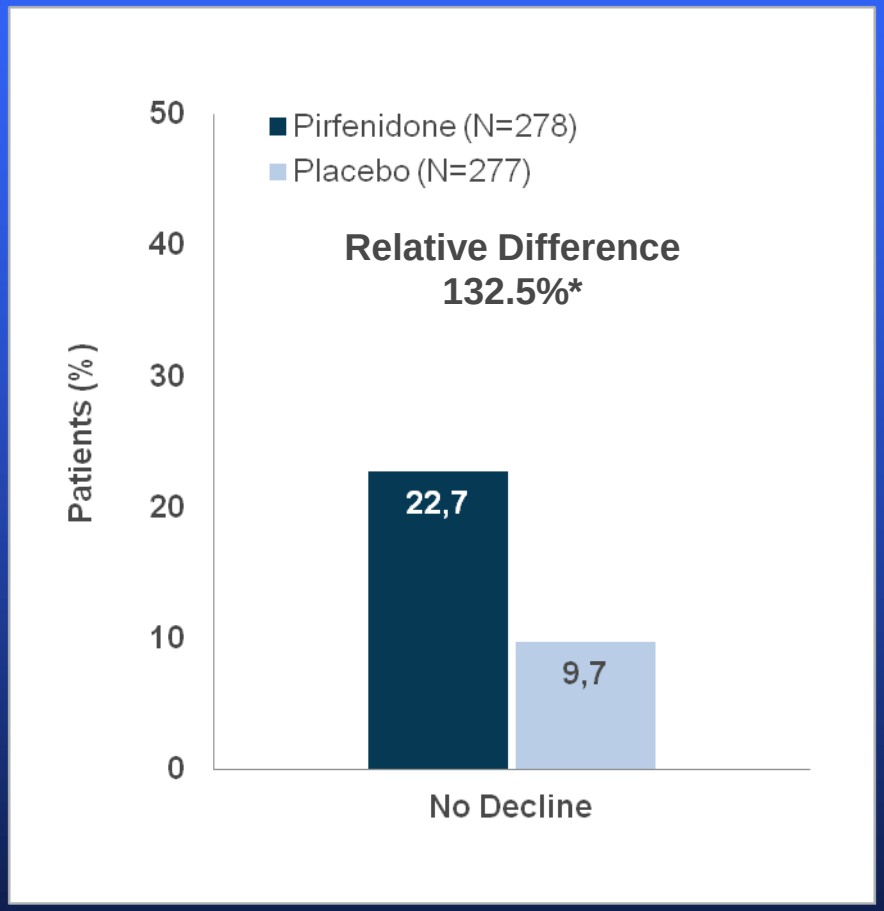
- Change in 6MWT distance (6MWD) from Baseline to Week 52
- Progression-free survival (PFS): defined as time to first occurrence of
  - Death;
  - Confirmed ≥10% decline in %FVC; or
  - Confirmed ≥50 m decline in 6MWD

* Tested for multiple comparisons using the Hochberg procedure

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# Primary Efficacy Analysis:
## %FVC Change at week 52

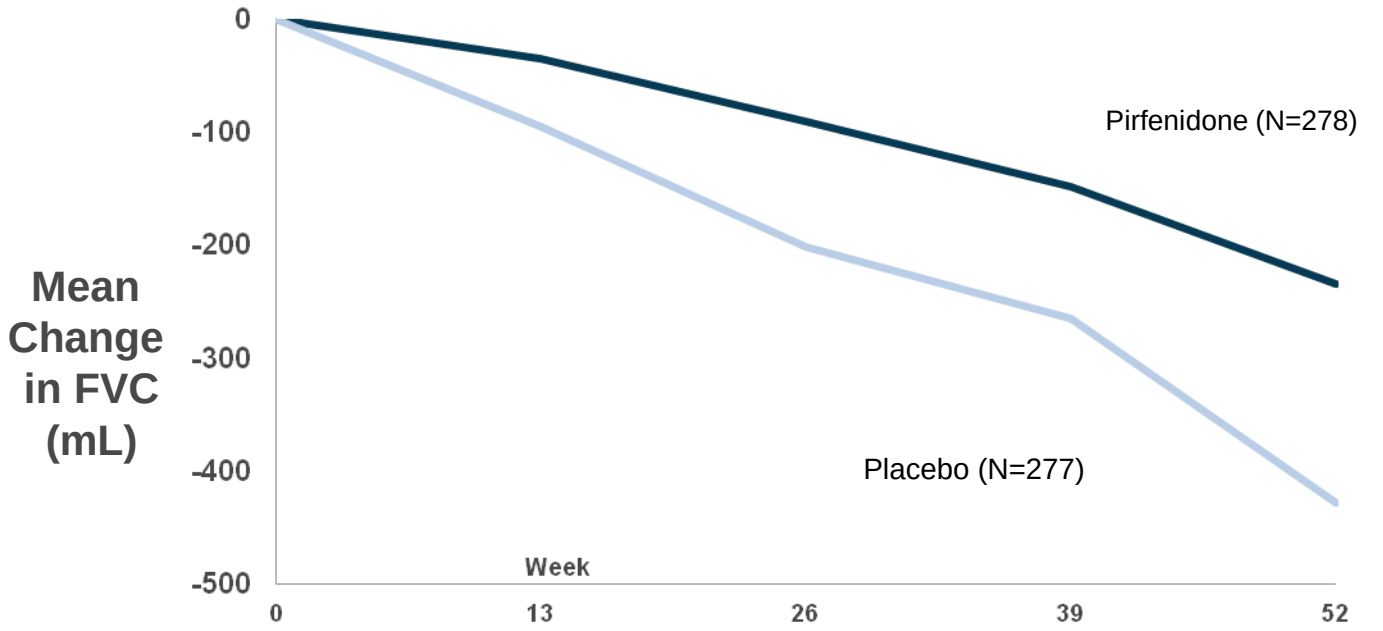



* Rank ANCOVA P-value <0.000001

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

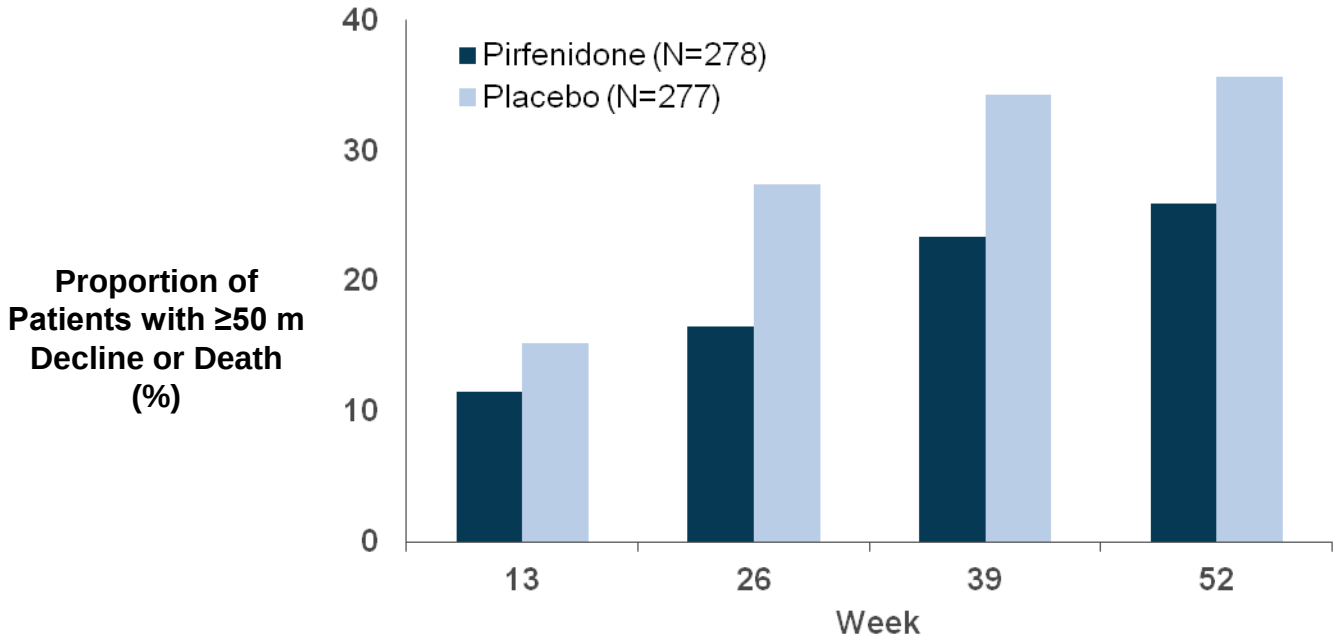
# Supportive Analyses of the Primary Endpoint Treatment group difference of 193 mL at week 52 – 45% relative riduction in the mean change in FVC




| | | | | |
|---|---|---|---|---|
| **Absolute difference** | **59.6 mL** | **111.0 mL** | **116.7 mL** | **192.8 mL** |
| **Relative difference** | **62.5%** | **54.9%** | **43.9%** | **45.1%** |
| **Rank ANCOVA P-value** | **<0.000001** | **<0.000001** | **0.000002** | **<0.000001** |

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# 6-MWT: Significant between-group difference in the change from baseline to week 52

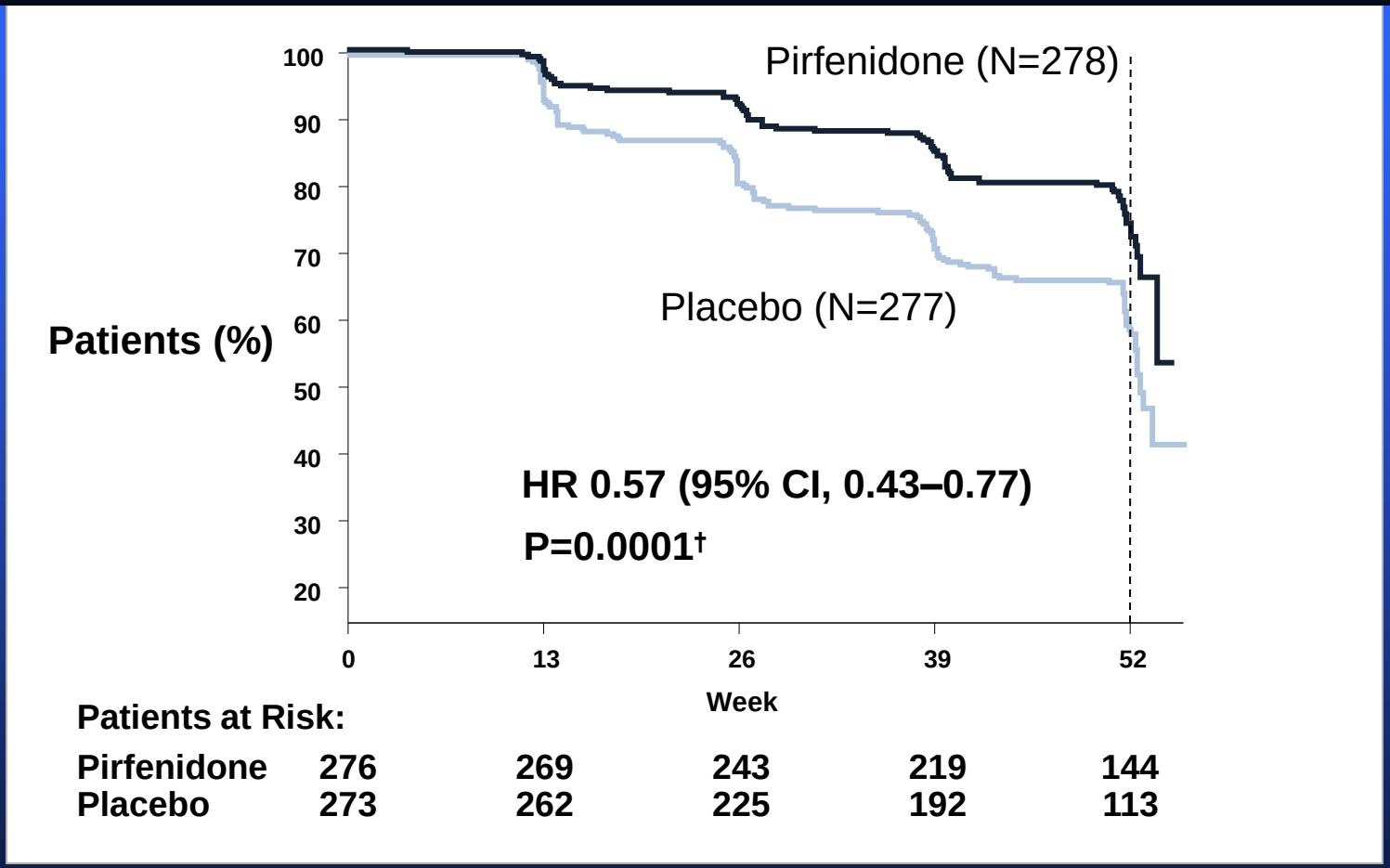



| | | | | |
|---|---|---|---|---|
| **Absolute Difference** | 3.7% | 10.9% | 10.9% | 9.8% |
| **Relative Difference** | 24.1% | 39.7% | 31.8% | 27.5% |
| **Rank ANCOVA p-value*** | 0.401 | 0.119 | 0.041 | 0.036 |

* Tested for multiple comparisons using the Hochberg procedure

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# Progression-free Survival (PFS)* : Pirfenidone reduced the risk of disease progression or death by 43%




* Time to death or disease progression (confirmed ≥10% decline in FVC or confirmed ≥50 m decline in 6MWD)
†Log-rank test

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

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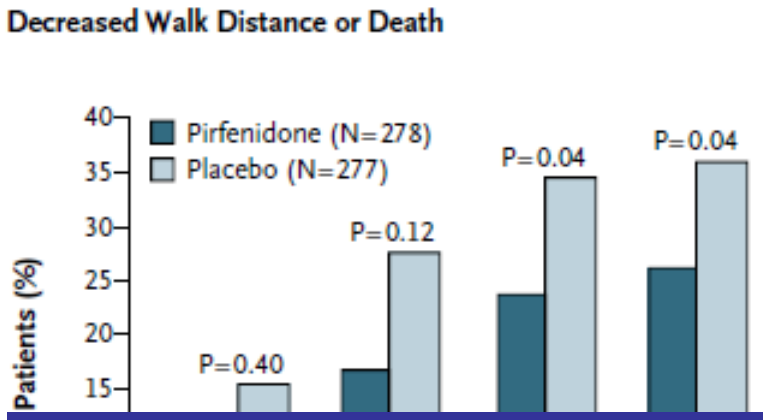
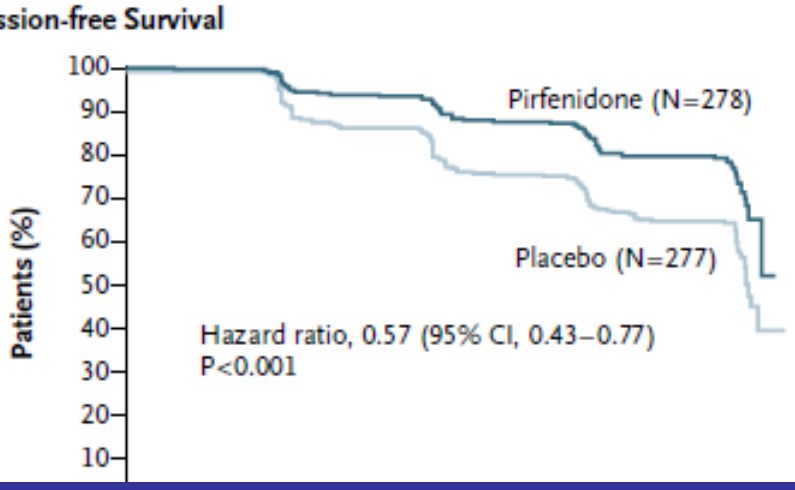



**Conclusions**: Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with IPF. Treatment was associated with an acceptable side effect profile and fewer deaths.

# ASCEND Study Treatment Emergent Adverse Events*: Fewer serious adverse events and fewer deaths in the pirfenidone group

| Patients, n (%) | Pirfenidone (N=278) | Placebo (N=277) |
|---|---|---|
| Any adverse event | 277 (99.6) | 272 (98.2) |
| Grade 3 | 58 (20.9) | 61 (22.0) |
| Grade 4 | 8 (2.9) | 14 (5.1) |
| Any serious adverse event (SAE) | 55 (19.8) | 69 (24.9) |
| Treatment-emergent death | 8 (2.9) | 15 (5.4) |
| Any AE leading to treatment D/C | 40 (14.4) | 30 (10.8) |

* Occurring during treatment period (from first dose up to 28 days after last dose of study drug)
† MedDRA system organ class

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# ASCEND Study
# Most Common Treatment Emergent Adverse Events*†

| Patients (%) | Pirfenidone (N=278) | Placebo (N=277) |
|---|---|---|
| Cough | 25.2 | 29.6 |
| Nausea | 36.0 | 13.4 |
| Headache | 25.9 | 23.1 |
| Diarrhea | 22.3 | 21.7 |
| Upper Respiratory Tract Infection | 21.9 | 20.2 |
| Fatigue | 20.9 | 17.3 |
| Rash | 28.1 | 8.7 |
| Dyspnea | 14.7 | 17.7 |
| Dizziness | 17.6 | 13.0 |
| Idiopathic pulmonary fibrosis | 9.4 | 18.1 |
| Bronchitis | 14.0 | 13.0 |
| Constipation | 11.5 | 13.7 |
| Back pain | 10.8 | 13.4 |
| Dyspepsia | 17.6 | 6.1 |
| Nasopharyngitis | 11.9 | 10.8 |
| Anorexia | 15.8 | 6.5 |
| Vomiting | 12.9 | 8.7 |
| Weight decreased | 12.6 | 7.9 |
| Gastroesophageal reflux | 11.9 | 6.5 |
| Insomnia | 11.2 | 6.5 |

Oc
†Coded to preferred terms in the Medical Dictionary for Regulatory Activities, version 11.0

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# ASCEND Study: GI and skin-related events were more common in the pirfenidone group

| Patients (%) | Pirfenidone (N=278) | Placebo (N=277) |
|---|---|---|
| Cough | 25.2 | 29.6 |
| Nausea | 36.0 | 13.4 |
| Headache | 25.9 | 23.1 |
| Diarrhea | 22.3 | 21.7 |
| Upper Respiratory Tract Infection | 21.9 | 20.2 |
| Fatigue | 20.9 | 17.3 |
| Rash | 28.1 | 8.7 |
| Dyspnea | 14.7 | 17.7 |
| Dizziness | 17.6 | 13.0 |
| Idiopathic pulmonary fibrosis | 9.4 | 18.1 |
| Bronchitis | 14.0 | 13.0 |
| Constipation | 11.5 | 13.7 |
| Back pain | 10.8 | 13.4 |
| Dyspepsia | 17.6 | 6.1 |
| Nasopharyngitis | 11.9 | 10.8 |
| Anorexia | 15.8 | 6.5 |
| Vomiting | 12.9 | 8.7 |
| Weight decreased | 12.6 | 7.9 |
| Gastroesophageal reflux | 11.9 | 6.5 |
| Insomnia | 11.2 | 6.5 |

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# ASCEND Study: Cough, dyspnea, and IPF worsening occurred with a greater frequency in the placebo group

| Patients (%) | Pirfenidone (N=278) | Placebo (N=277) |
|---|---|---|
| Cough | 25.2 | 29.6 |
| Nausea | 36.0 | 13.4 |
| Headache | 25.9 | 23.1 |
| Diarrhea | 22.3 | 21.7 |
| Upper Respiratory Tract Infection | 21.9 | 20.2 |
| Fatigue | 20.9 | 17.3 |
| Rash | 28.1 | 8.7 |
| Dyspnea | 14.7 | 17.7 |
| Dizziness | 17.6 | 13.0 |
| Idiopathic pulmonary fibrosis | 9.4 | 18.1 |
| Bronchitis | 14.0 | 13.0 |
| Constipation | 11.5 | 13.7 |
| Back pain | 10.8 | 13.4 |
| Dyspepsia | 17.6 | 6.1 |
| Nasopharyngitis | 11.9 | 10.8 |
| Anorexia | 15.8 | 6.5 |
| Vomiting | 12.9 | 8.7 |
| Weight decreased | 12.6 | 7.9 |
| Gastroesophageal reflux | 11.9 | 6.5 |
| Insomnia | 11.2 | 6.5 |

Oc[illegible] of patients in either treatment group

†Coded to preferred terms in the Medical Dictionary for Regulatory Activities, version 11.0

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# Pooled All-cause Mortality (week 52): Pirfenidone reduced risk of death by 48%

| Patients | Pirfenidone | Placebo | HR (95% CI)‡ | P-value § |
|---|---|---|---|---|
| **ASCEND*** (N=555) | 11 (4.0%) | 20 (7.2%) | 0.55 (0.26–1.15) | 0.105 |
| **CAPACITY†** (N=692) | 11 (3.2%) | 22 (6.3%) | 0.49 (0.24,1.01) | 0.047 |
| **Pooled*** (N=1247) | 22 (3.5%) | 42 (6.7%) | 0.52 (0.31–0.87) | 0.011 |

HR=hazard ratio; 95% CI=95% confidence interval
* Pre-specified secondary endpoint in ASCEND
† Exploratory analysis in CAPACITY
‡ Cox proportional hazards model
§ Log-rank test

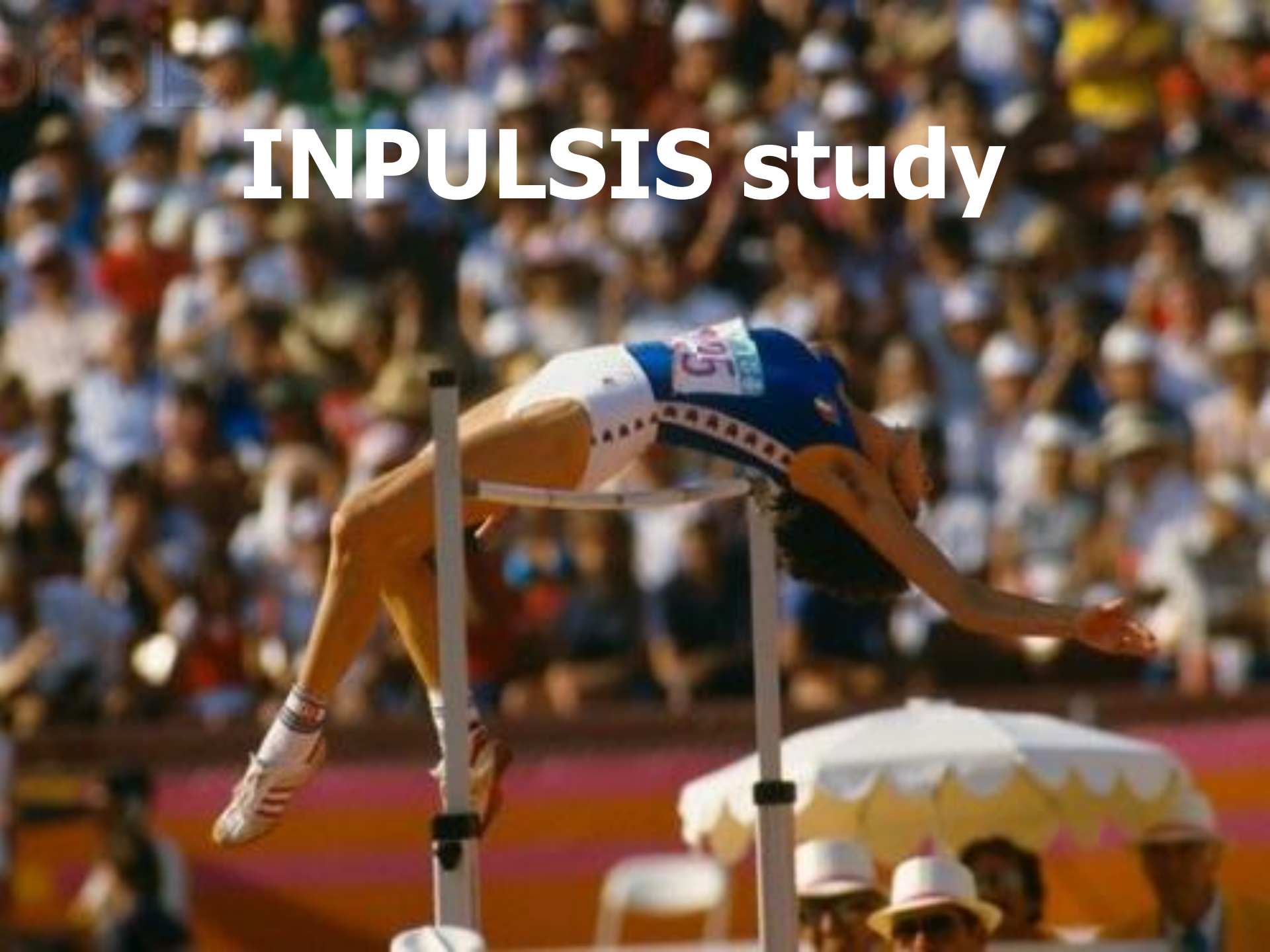
King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

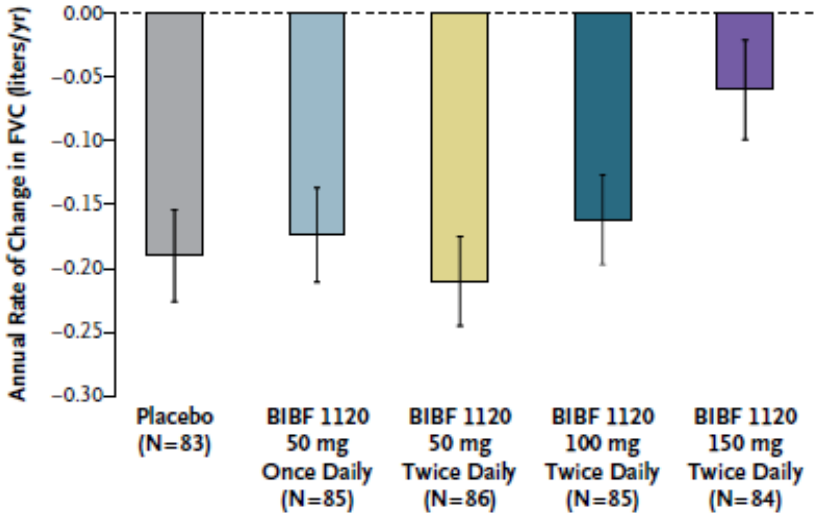
# ASCEND Study Summary

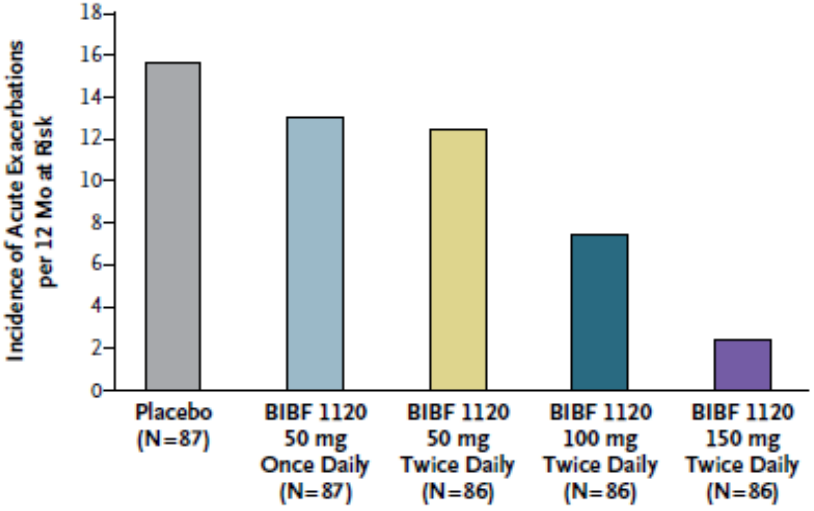
- Treatment with pirfenidone for 52 weeks significantly reduced disease progression, as measured by
  - Changes in % predicted FVC ($p<0.000001$)
  - Changes in 6-minute walk distance ($p=0.036$)
  - Progression-free survival ($p<0.001$)
- Treatment with pirfenidone reduced all-cause mortality and treatment emergent IPF-related mortality in pooled analyses at week 52.
- Pirfenidone was generally safe and well tolerated.

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

# INPULSIS study





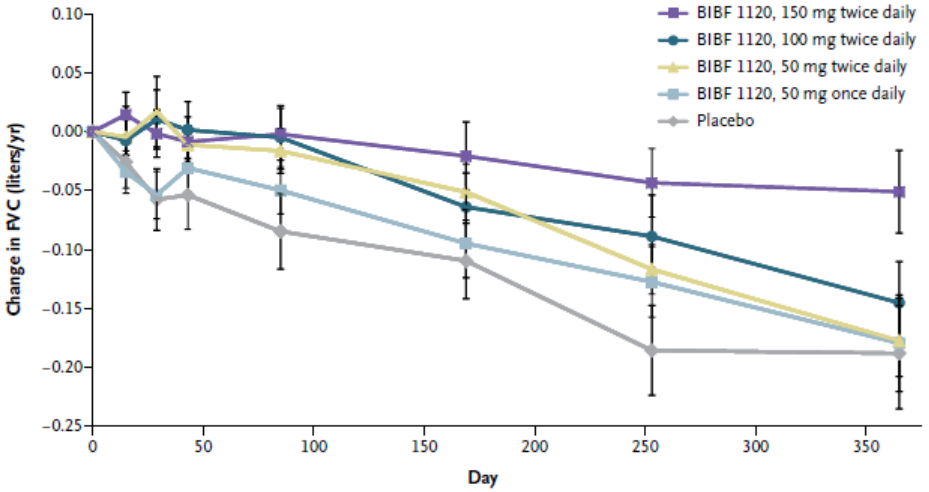




The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 22, 2011 VOL. 365 NO. 12

# Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Ulrich Costabel, M.D., Moises Selman, M.D., Dong Soon Kim, M.D., David M. Hansell, M.D., Andrew G. Nicholson, D.M., Kevin K. Brown, M.D., Kevin R. Flaherty, M.D., Paul W. Noble, M.D., Ganesh Raghu, M.D., Michèle Brun, M.Sc., Abhya Gupta, M.D., Nolwenn Juhel, M.Sc., Matthias Klüglich, M.D., and Roland M. du Bois, M.D.




| | 0 | 15 | 29 | 43 | 85 | 169 | 253 | 365 |
|---|---|---|---|---|---|---|---|---|
| **No. of Patients** | | | | | | | | |
| Total | 432 | 419 | 416 | 415 | 398 | 385 | 372 | 317 |
| Placebo | 87 | 81 | 82 | 82 | 80 | 79 | 74 | 61 |
| 50 mg once daily | 87 | 85 | 82 | 80 | 78 | 72 | 71 | 61 |
| 50 mg twice daily | 86 | 85 | 86 | 86 | 82 | 81 | 80 | 71 |
| 100 mg twice daily | 86 | 84 | 84 | 84 | 80 | 82 | 79 | 67 |
| 150 mg twice daily | 86 | 84 | 82 | 83 | 78 | 71 | 68 | 57 |

N Engl J Med 2011; 365: 1079

# Conclusions

In patients with IPF, BIBF 1120 at a dose of 150 mg twice daily, as compared with placebo, was associated with a trend toward a reduction in the decline in lung function, with fewer acute exacerbations and preserved quality of life.

The results of this phase 2 study showed an acceptable safety profile and potential clinical benefits of treatment with 150 mg of BIBF 1120 twice a day in patients with IPF.
These results warrant the investigation of BIBF 1120 in phase 3 clinical studies.

N Engl J Med 2011; 365: 1079

# *Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis*

*NEJM 2014*

Two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) was conducted to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with IPF.

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo.

This article was published on May 18, 2014, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

- Age ≥40 years
- Diagnosis of IPF within 5 years of randomization
- Chest HRCT performed within 12 months of screening
- HRCT pattern, and, if available, surgical lung biopsy pattern, consistent with diagnosis of IPF, as assessed centrally by one expert radiologist and one expert pathologist
- FVC ≥50% of predicted value
- $DL_{CO}$ 30–79% of predicted value

## Primary endpoint

- Annual rate of decline in FVC (mL/year)

## Key secondary endpoints

- Time to first acute exacerbation (investigator-reported) over 52 weeks
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 52 weeks

## *UIP pattern (all four):*

Sub-pleural, basal predominance

Reticular abnormality

Honeycombing with or without traction bronchiectasis

Absence of features listen as inconsistent with UIP

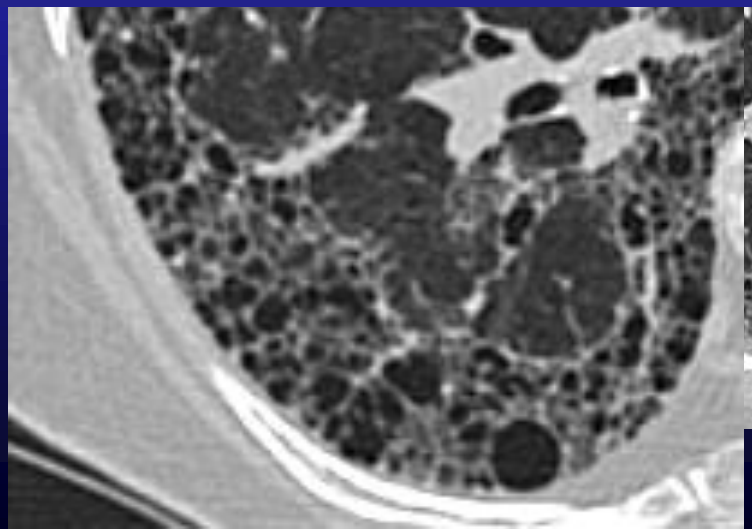
## *Possible UIP pattern (all three):*

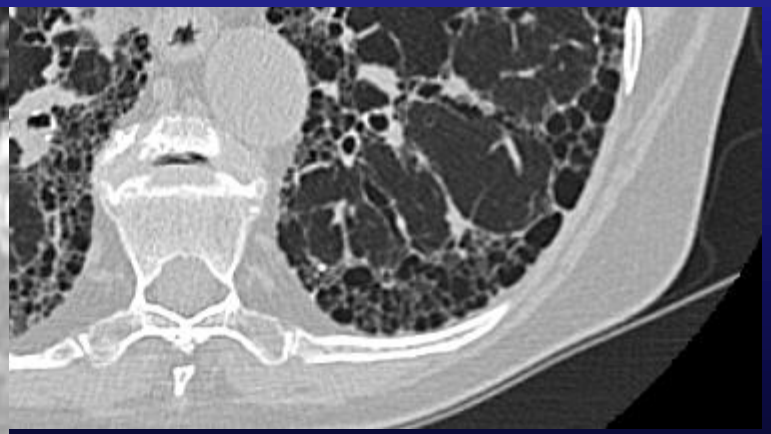
Subpleural, basal predominance

Reticular abnormality

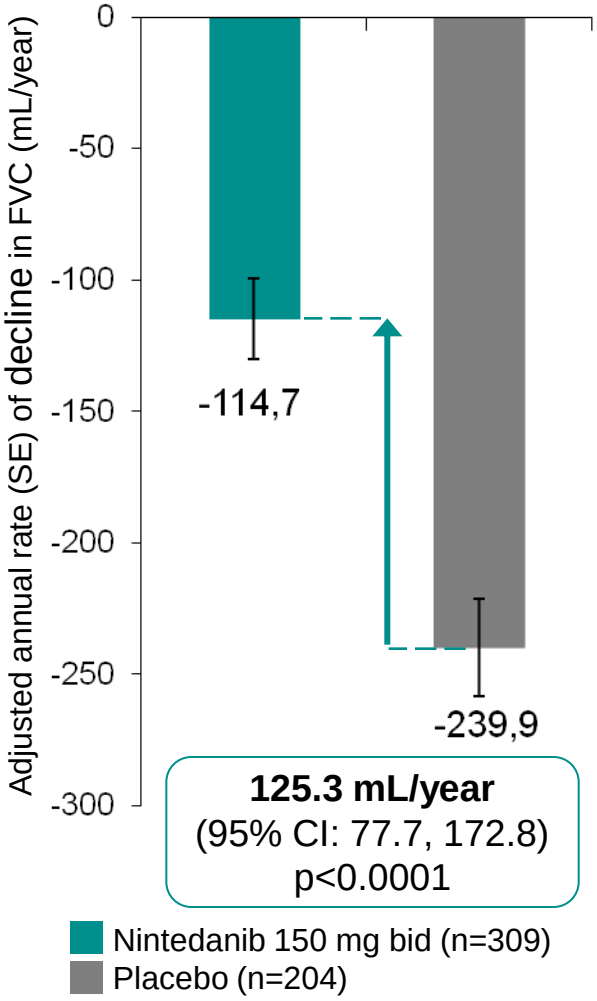
Absence of features listen as inconsistent with UIP

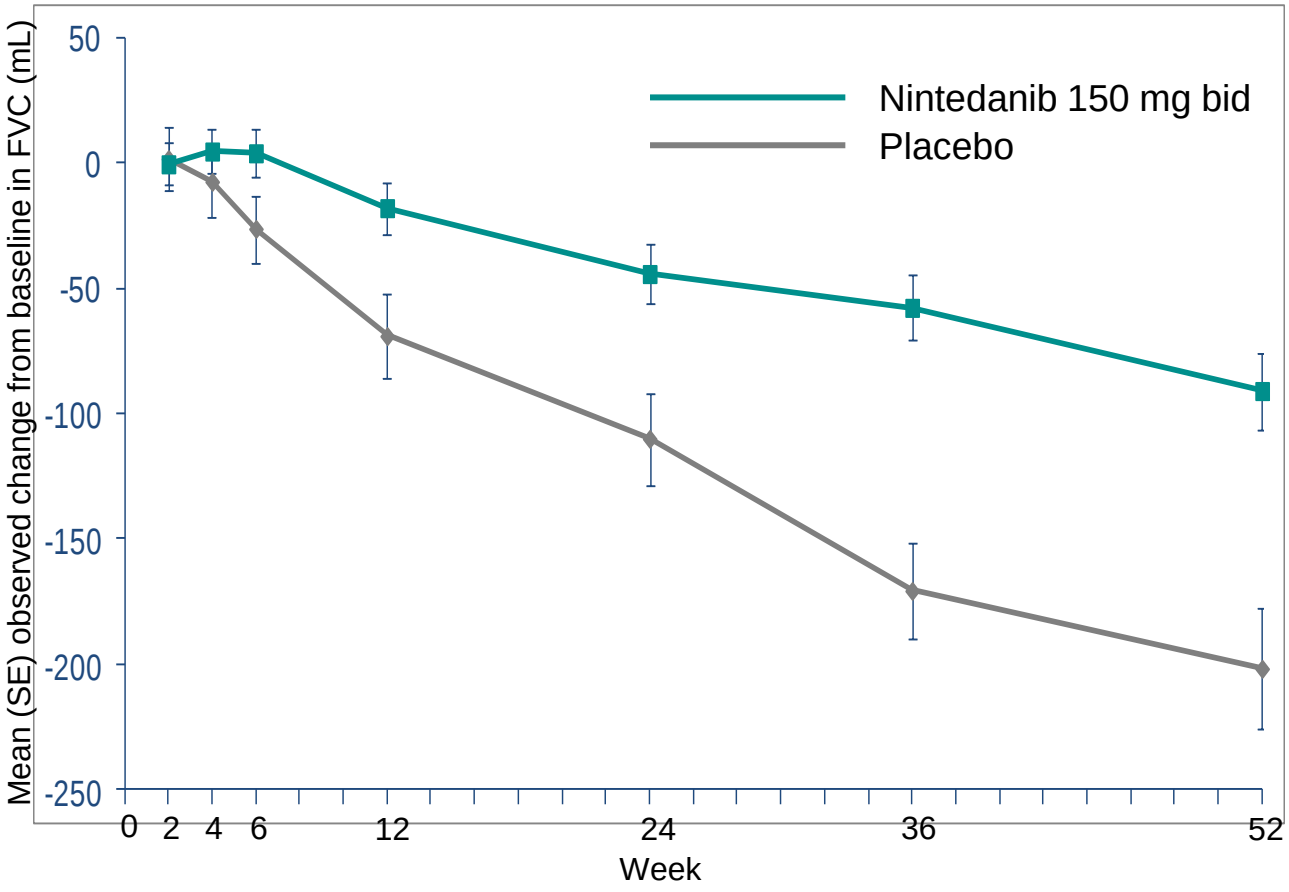
***Am J Respir Crit Care Med* 2011; 183: 788-824**





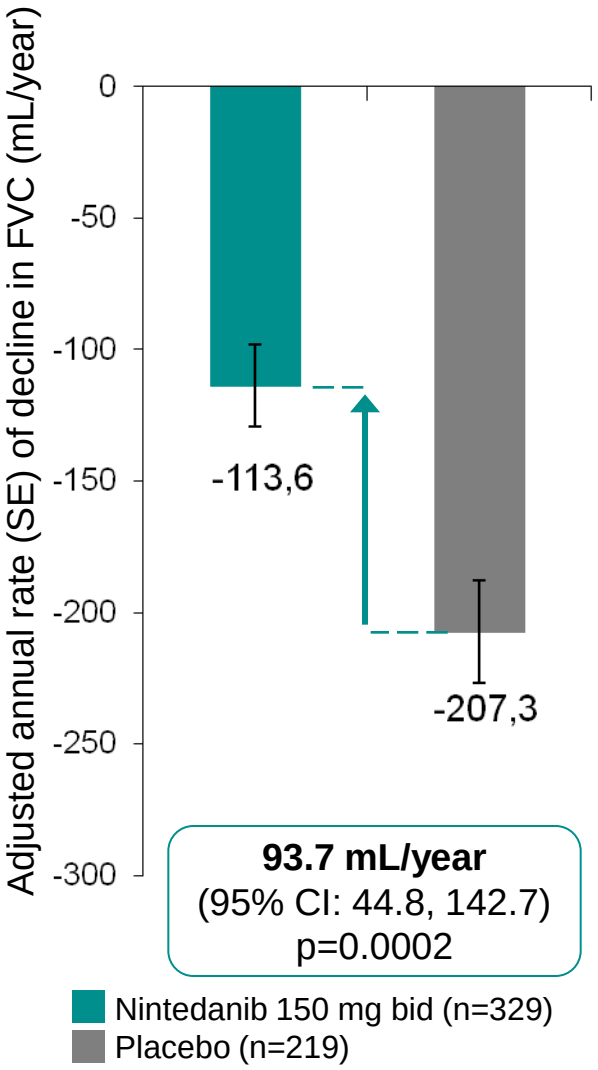
# *Primary efficacy endpoint in INPULSIS-1*

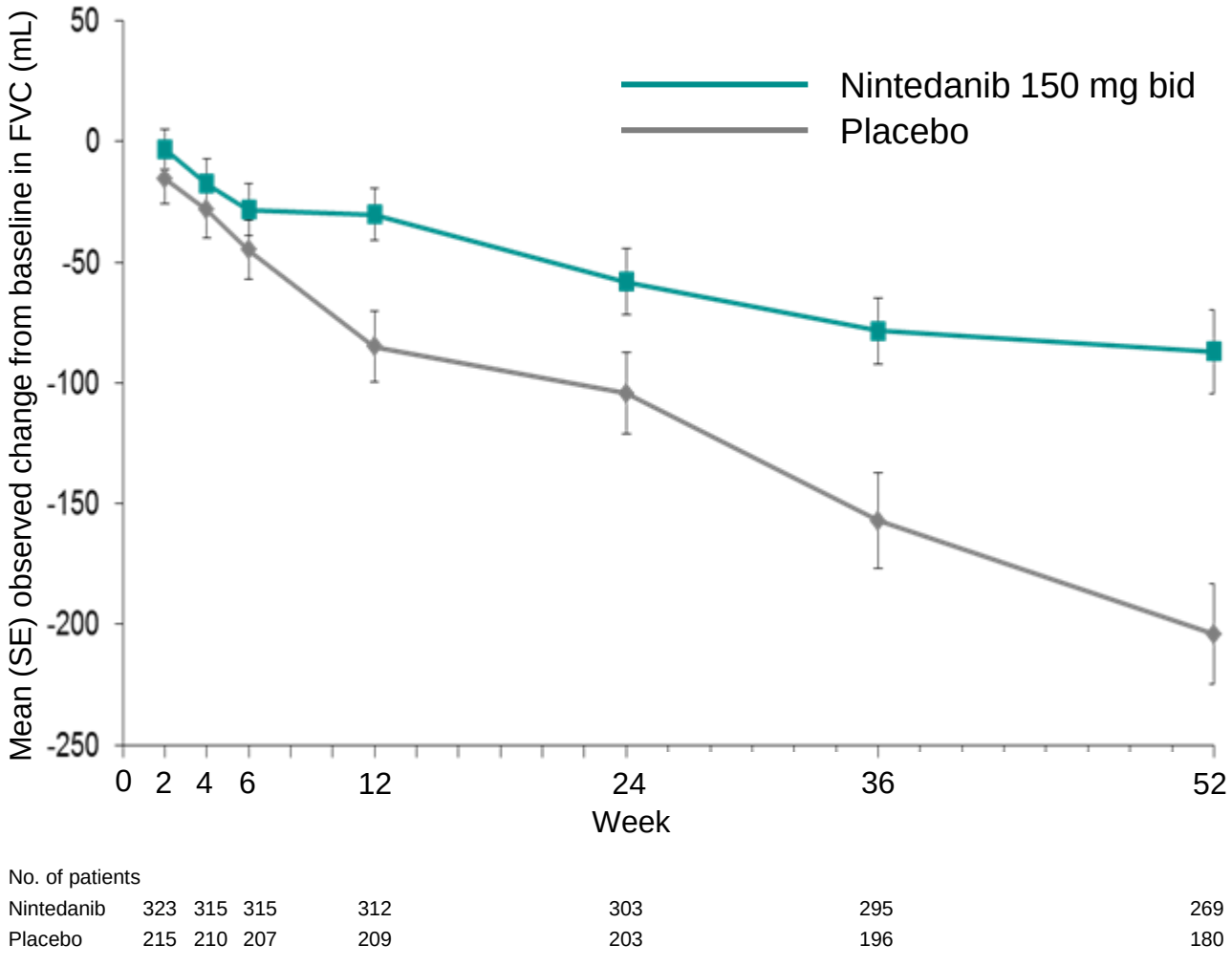


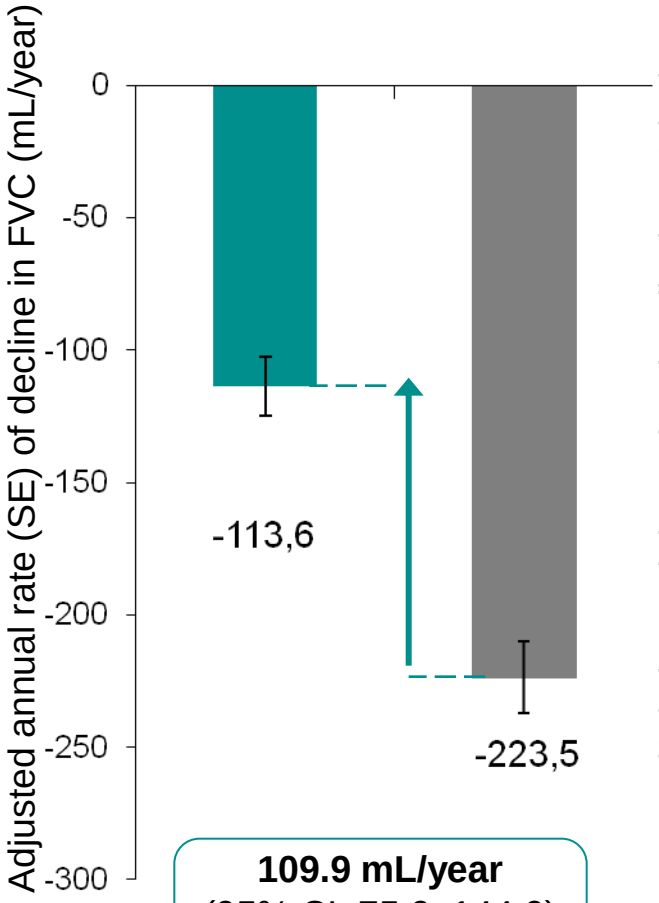

| No. of patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nintedanib | 303 | 301 | 298 | 292 | 284 | 274 | 250 |
| Placebo | 202 | 198 | 200 | 194 | 192 | 187 | 165 |

# *Primary efficacy endpoint in INPULSIS-2*



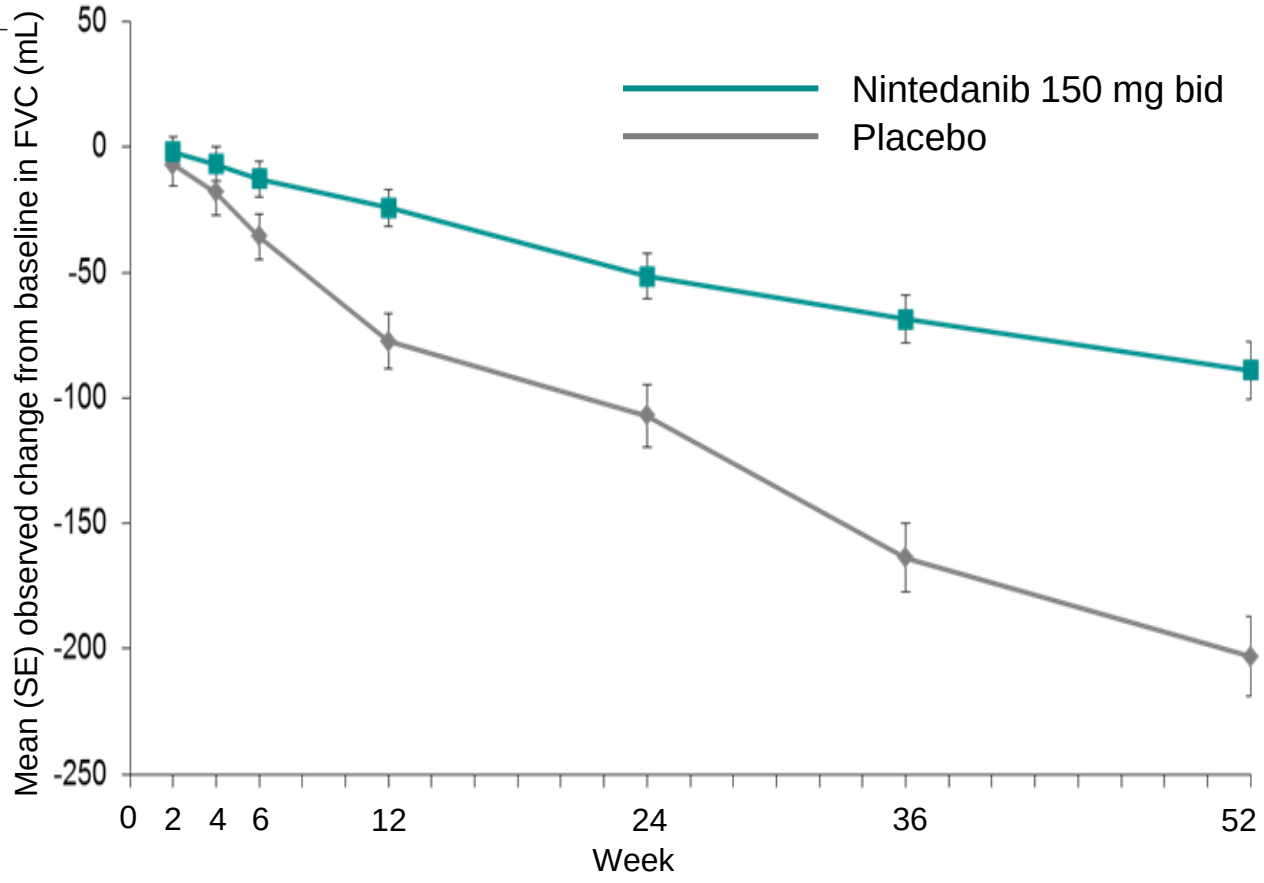



# *Primary efficacy endpoint in pooled data*



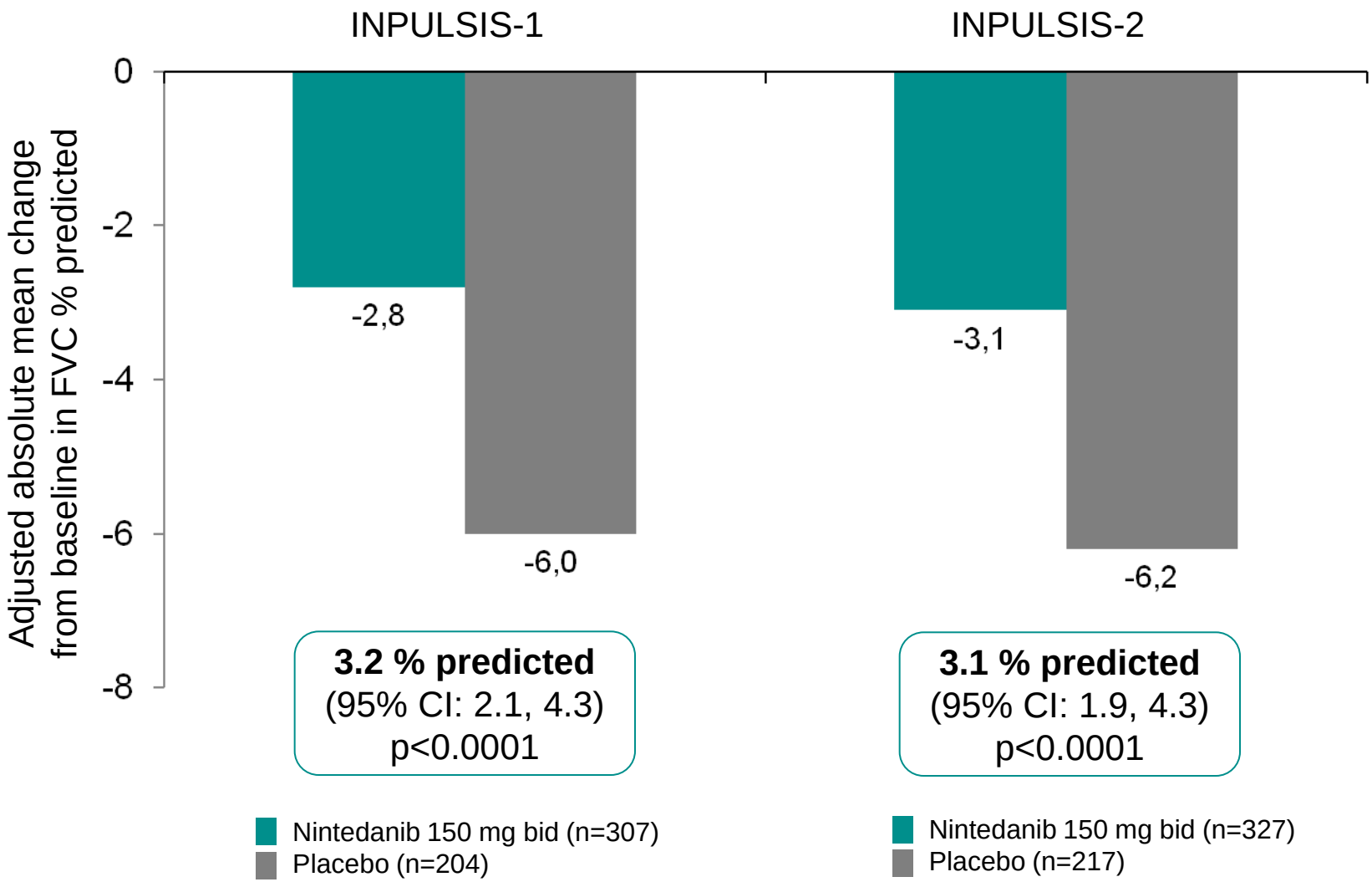

**109.9 mL/year**
(95% CI: 75.9, 144.0)
p<0.0001

Nintedanib 150 mg bid (n=638)
Placebo (n=423)

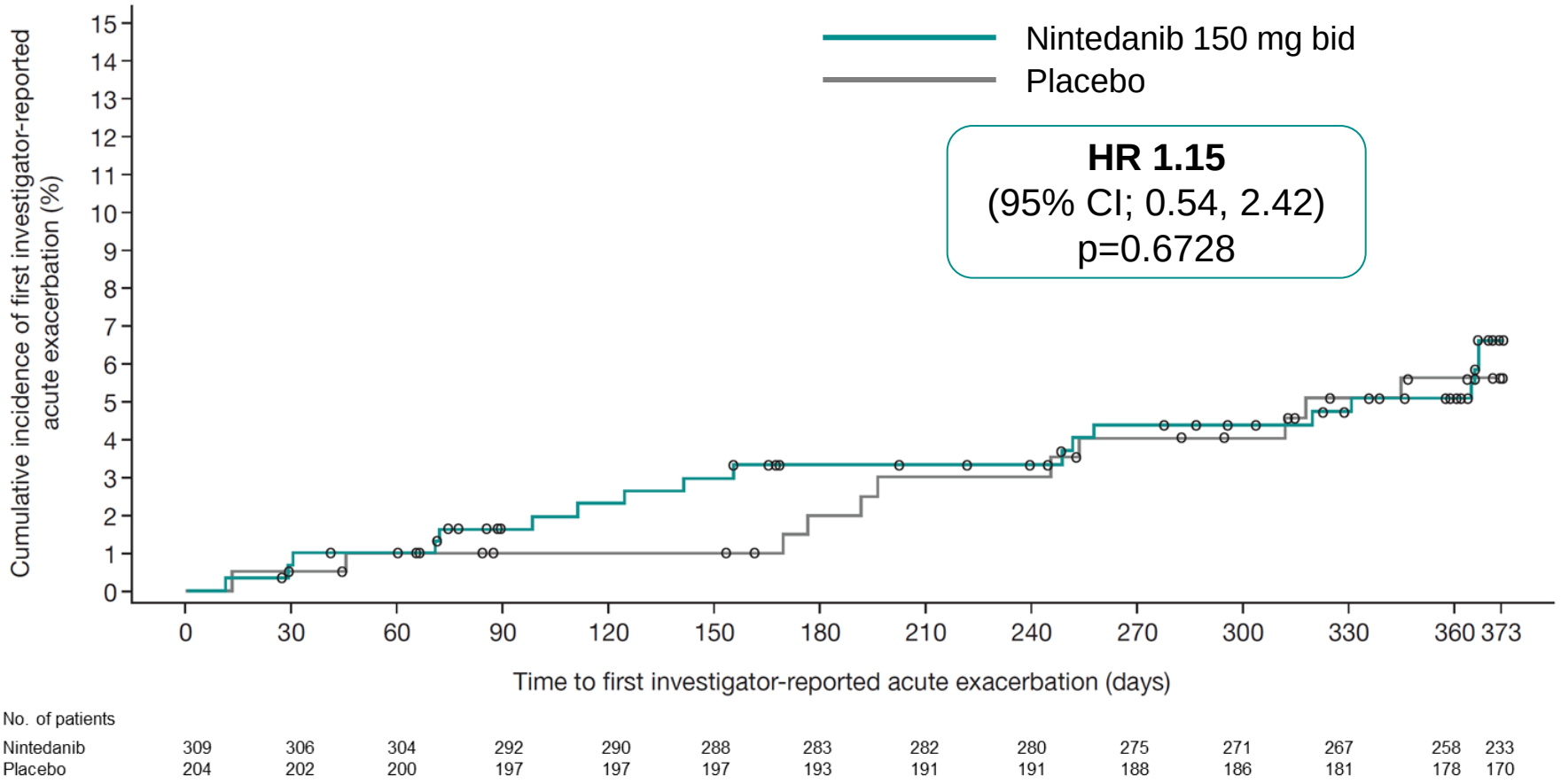



| No. of patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nintedanib | 626 | 616 | 613 | 604 | 587 | 569 | 519 |
| Placebo | 417 | 408 | 407 | 403 | 395 | 383 | 345 |

# *Absolute changes from Baseline in FVC % predicted at week 52*

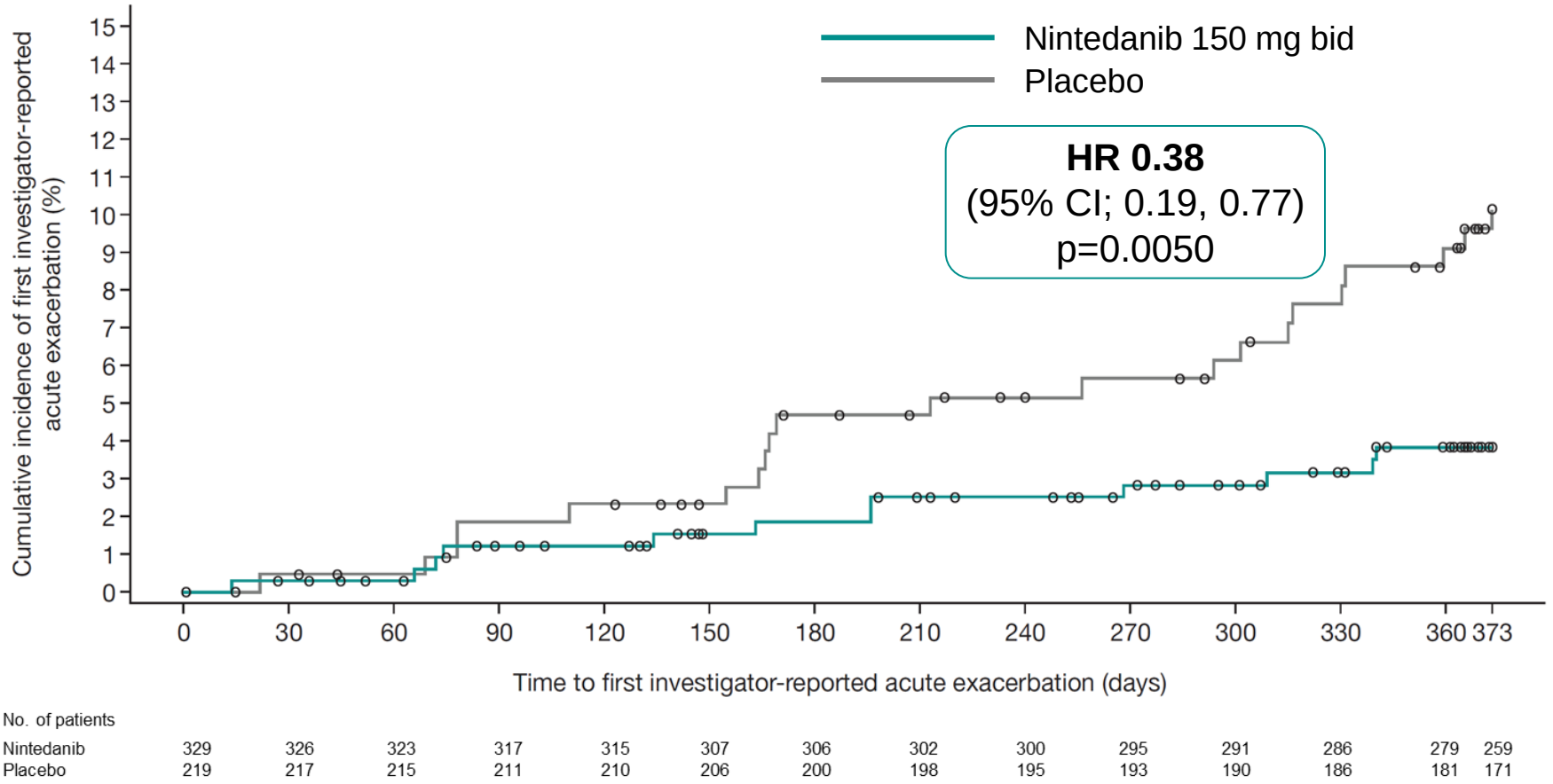


# TIME TO FIRST ACUTE EXACERBATION (INVESTIGATOR-REPORTED) IN INPULSIS-1



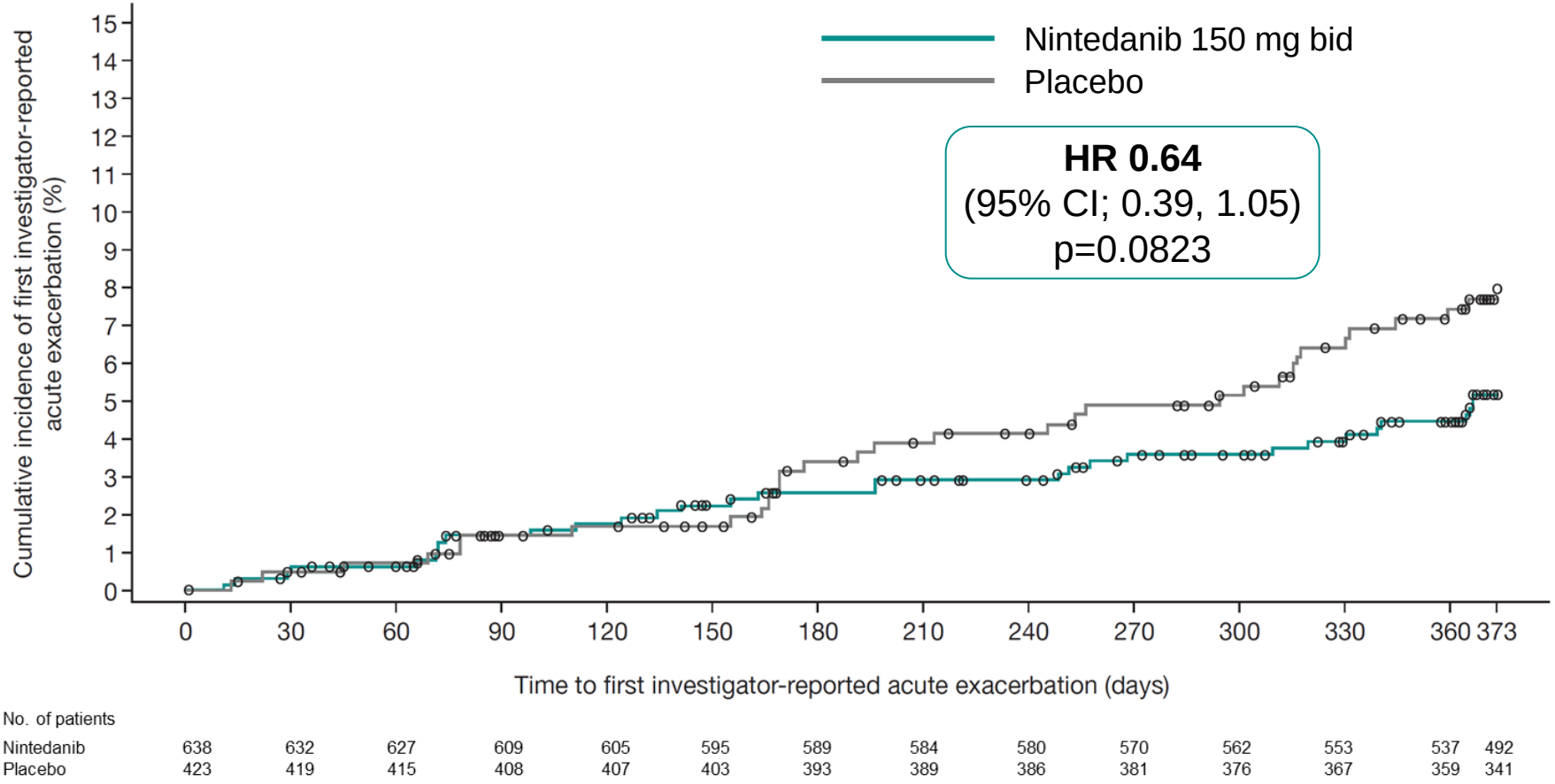

| | Nintedanib 150 mg bid (n=309) | Placebo (n=204) |
|---|---|---|
| Patients with ≥1 acute exacerbation, n (%) | 19 (6.1) | 11 (5.4) |

# TIME TO FIRST ACUTE EXACERBATION (INVESTIGATOR-REPORTED) IN INPULSIS-2




| | Nintedanib 150 mg bid (n=329) | Placebo (n=219) |
|---|---|---|
| Patients with ≥1 acute exacerbation, n (%) | 12 (3.6) | 21 (9.6) |

# TIME TO FIRST ACUTE EXACERBATION (INVESTIGATOR-REPORTED) IN POOLED DATA



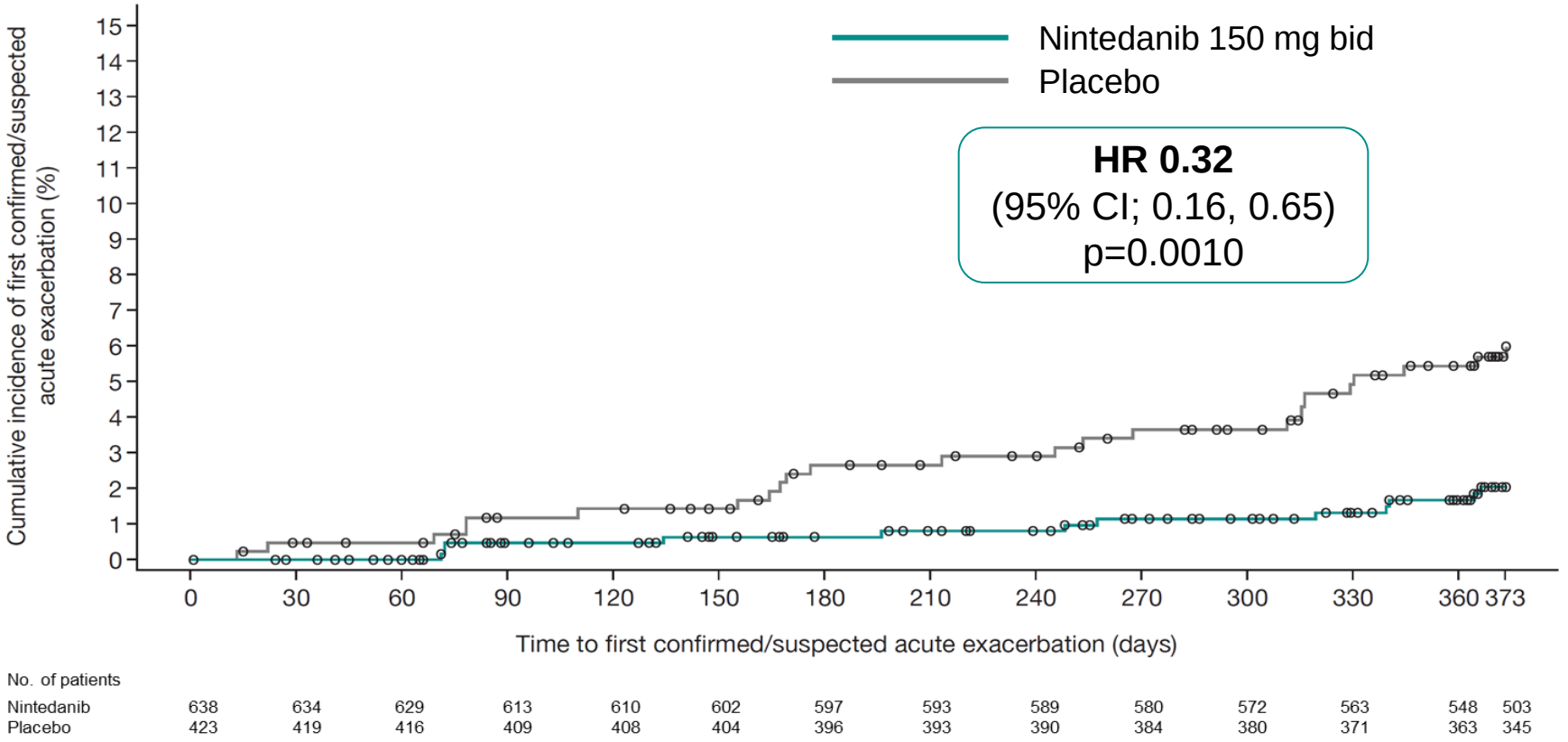

| | Nintedanib 150 mg bid (n=638) | Placebo (n=423) |
|---|---|---|
| Patients with ≥1 acute exacerbation, n (%) | 31 (4.9) | 32 (7.6) |

# Adjudication of acute exacerbations

- The adjudication committee categorized the investigator-reported acute exacerbations according to pre-specified criteria[1]:
  - Confirmed acute exacerbation
  - Suspected acute exacerbation
  - Not an acute exacerbation
- The adjudication committee was blinded to treatment allocation and events were adjudicated before database lock and data unblinding

1. Collard HR, et al. Am J Respir Crit Care Med 2007;176:636–643

# TIME TO FIRST CONFIRMED OR SUSPECTED ACUTE EXACERBATION PER ADJUDICATION (PRESPECIFIED SENSITIVITY ANALYSIS OF POOLED DATA)




| | Nintedanib 150 mg bid (n=638) | Placebo (n=423) |
|---|---|---|
| Patients with ≥1 acute exacerbation, n (%) | 12 (1.9) | 24 (5.7) |

# MOST FREQUENT ADVERSE EVENTS*

| | INPULSIS-1 | | INPULSIS-2 | |
|---|---|---|---|---|
| **No of patients (%)** | **Nintedanib 150 mg bid (n=309)** | **Placebo (n=204)** | **Nintedanib 150 mg bid (n=329)** | **Placebo (n=219)** |
| Diarrhea | 190 (61.5) | 38 (18.6) | 208 (63.2) | 40 (18.3) |
| Nausea | 70 (22.7) | 12 (5.9) | 86 (26.1) | 16 (7.3) |
| Nasopharyngitis | 39 (12.6) | 34 (16.7) | 48 (14.6) | 34 (15.5) |
| Cough | 47 (15.2) | 26 (12.7) | 38 (11.6) | 31 (14.2) |
| Progression of IPF† | 31 (10.0) | 21 (10.3) | 33 (10.0) | 40 (18.3) |
| Bronchitis | 36 (11.7) | 28 (13.7) | 31 (9.4) | 17 (7.8) |

***INPULSIS***

In both trials, a higher proportion of patients in the nintedanib groups than in the placebo groups had elevated levels of liver enzymes

Myocardial infarction was reported in 10 treated patients and in 2 in the placebo group

# *Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis*

In patients with IPF nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients

# From clinical trials to real life: an italian experience

# IPF and Pirfenidone

A multicenter, observational, nation-wide, retrospective study to evaluate disease progression in patients with IPF before and during therapy with Pirfenidone

# *Design of the study*

- Observational, multicentric, nation-wide, retrospective study about the progression of functional parameters in IPF patients before and after therapy with Pirfenidone
- Population:
  - Diagnosis: confirmed by HRCT UIP pattern and/or surgical lung biopsy (according to 2011 IPF guidelines);
  - Mild/moderate and severe stage disease, according to guidelines classification;
  - Availability of functional follow-up data at least 6 months before and 6 months after the start of Pirfenidone therapy

# *Objectives*

Evaluation of the introduction of pirfenidone therapy on the natural slope of decline of FVC and DlCO in pts observed for at least 6 months before and during Tx, independently from previous Tx

# Table 1. Patients' characteristics at baseline – first pirfenidone prescription (N=128)

| Variable | Levels | N (%) |
|---|---|---|
| Center | Catania | 14 (10.9) |
| | Forlì | 13 (10.2) |
| | Milano | 12 (9.4) |
| | Modena | 9 (7.0) |
| | Monza | 9 (7.0) |
| | Napoli | 2 (1.6) |
| | Padova | 7 (5.5) |
| | Roma Saltini | 8 (6.3) |
| | Roma Sebastiani | 5 (3.9) |
| | Siena | 6 (4.7) |
| | Torino | 18 (14.1) |
| | Trieste | 25 (19.5) |
| Gender | Female | 32 (25.0) |
| | Male | 96 (75.0) |

| Variable | Levels | N (%) |
|---|---|---|
| Age at baseline (years)* | <=60 | 17 (13.3) |
| | 61-65 | 20 (15.6) |
| | 65+ | 91 (71.1) |
| Smoking status | Ex-smoker | 97 (75.8) |
| | Non smoker | 27 (21.1) |
| | Smoker | 4 (3.1) |
| Histological diagnosis | No | 96 (75.0) |
| | Yes | 32 (25.0) |
| Clinical/Radiological diagnosis | Uncertain | 20 (15.6) |
| | No | 3 (2.3) |
| | Yes | 105 (82.0) |
| Steroids | No | 53 (41.4) |
| | Yes | 75 (58.6) |
| Azathioprine | No | 97 (75.8) |
| | Yes | 31 (24.2) |
| N-Acetylcysteine | No | 75 (58.6) |
| | Yes | 53 (41.4) |

***Mean age 69 years SD 7 years**

# *Conclusions*

- In the IPF population:
  - Pirfenidone reduced the slope of decrease of FVC%
  - No significant reduction of the decrease of DlCO was observed
  - The study suggest a possible positive effect of Pirfenidone also in moderate/severe pts;

# The future?

*Phase 2 study*: GS-6624, a humanized antibody, is capable of inhibiting LOXL2 enzymatic activity and potentially may have therapeutic activity in diseases that involve fibroblast activation and recruitment and pathologic stroma formation.

*Phase II study*: Lebrikizumab is a humanized monoclonal antibody (huIgG4) with a mutation in the hinge region for increased stability. It binds specifically to soluble IL-13 with high affinity and neutralizes its functional activities with high potency

# *Clinical Trials.gov*

Search for: Idiopathic pulmonary fibrosis

61 studies open

Allogeneic Human Cells (hMSC) in Patients with Idiopathic Pulmonary Fibrosis via Intravenous Delivery (AETHER)

Study of Autologous Mesenchymal Stem Cells to Treat Idiopathic Pulmonary Fibrosis

A Phase 2 Randomized Dos-ranging Study to Evaluate the Efficacy of  Tralokinumab in Adults with Idiopathic Pulmonary Fibrosis

Safety and Efficacy of a Lysophosphatidic Acid Receptor Antagonist in Idiopathic Pulmonary Fibrosis

Evaluate Safety and Efficacy of FG-3019 in Patients with Idiopathic Pulmonary Fibrosis

# Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial

Shulgina L, et al. Thorax 2013; 68:155

The addition of co-trimoxazole therapy to standard treatment for fibrotic idiopathic interstitial pneumonia had no effect on lung function but resulted in improved quality of life and a reduction in mortality in those adhering to treatment.

# Stem cell therapy for idiopathic pulmonary fibrosis: a protocol proposal

Bouros D et al. J Transplant 2011; 9:182

Preliminary results seem promising and tantalizing since there were no cases of clinically significant allergic reactions, infections, disease acute exacerbations or ectopic tissue formation. In addition 6 months follow-up data revealed a marginal improvement at 6-MWD and FVC

Adipose tissue represents an abundant, safe, ethically uncontested and potentially beneficial source of stem cells for patients with IPF. Larger multicenter phase II and III placebo-controlled clinical trials are sorely needed in order to prove efficacy. However, pilot safety studies are of major importance and represent the first hamper that should be overcome to establish a rigid basis for larger clinical trials.

# The goals of effective IPF management

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

- Pulmonary Rehab.
- Oxygen

**New approaches needed??**

**Experimental therapy in a RCT**

**Pirfenidone - Nintedanib mild/moderate IPF**

**Lung TX - Pirfenidone**

**These goals should be reached with a minimum of side effects from treatment**

# *Conclusions*

- The recents advances in the knowledge of the pathogenesis of IPF open the door to new perspectives and new hopes
- Physicians should encourage the participation in clinical trials
- Pirfenidone available for mild/moderate IPF in EU
- Nintedanib? Waiting for approval
- Sequential ( how ?) and/or combination therapy
- Advance IPF : looking for therapies
- **Lung transplantation** is a feasible option for selected patients with IPF

# 6TH

# INTERNATIONAL MEETING ON PULMONARY RARE DISEASES AND ORPHAN DRUGS


MILANO – ITALY
CONGRESS CENTER
PALAZZO DELLE STELLINE

**FEBRUARY**
**27-28, 2015**