Pirfenidone, its role in IPF treatment

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Disclosure Statement

Dr. Costabel has served on a Scientific Advisory Board for the following companies:

- Actelion
- Boehringer Ingelheim
- Centocor
- Gilead
- InterMune
- Roche
- Wyeth
- Zambon

Ground breaking news on IPF at the recent ATS meeting

IPF therapy has entered a new era

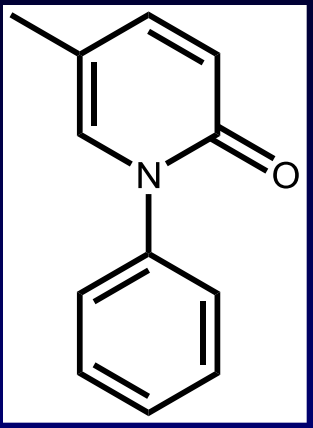
First Antifibrotic Therapy of IPF

Pirfenidone

Pirfenidone

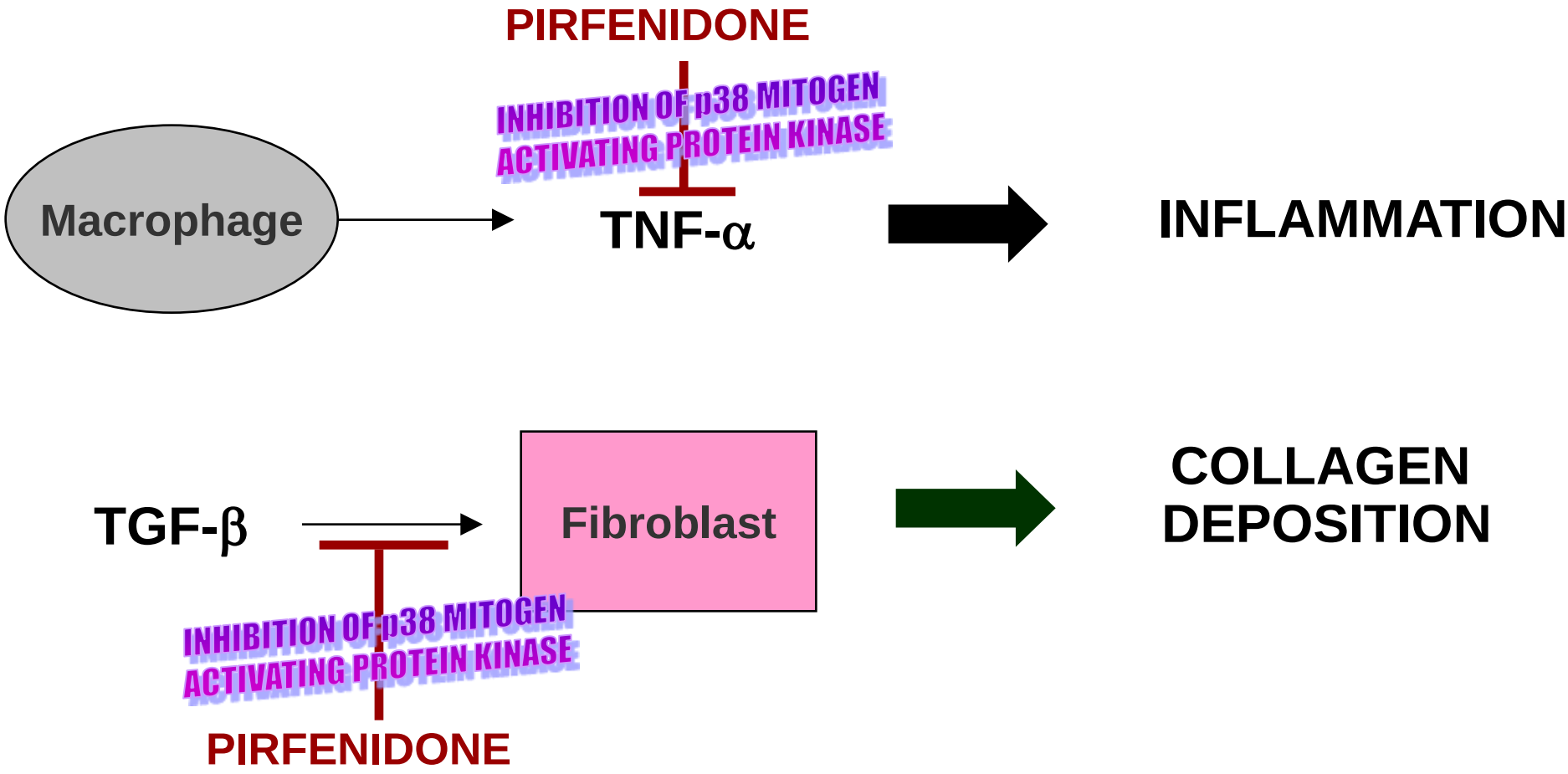
Preclinical Characterization

Pirfenidone: Key Points



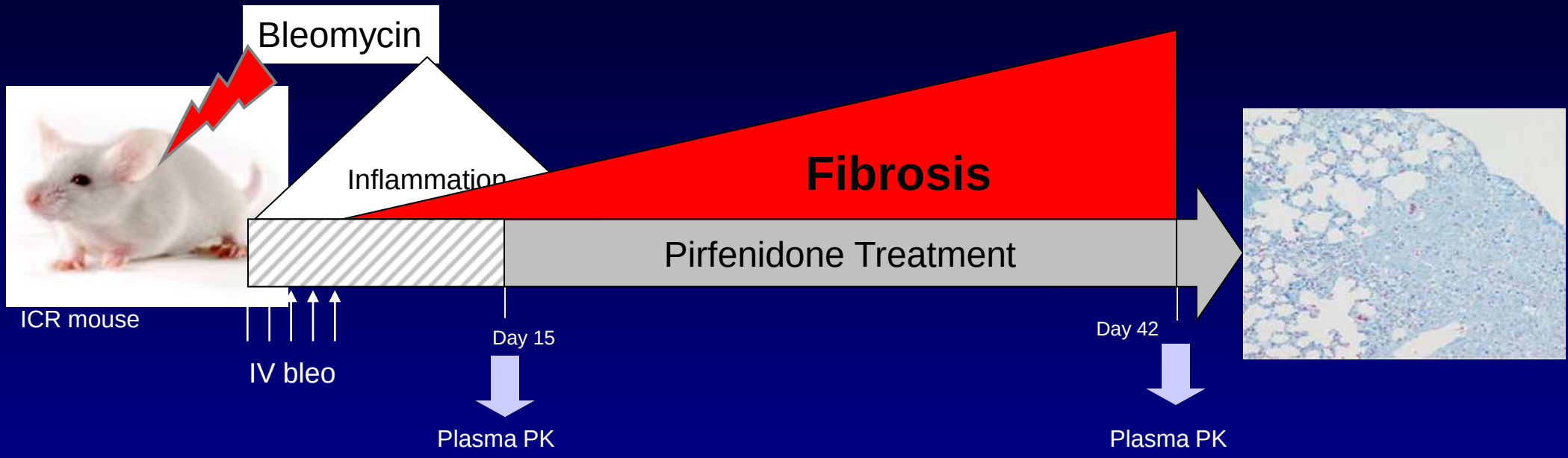
- Pirfenidone is an orally-available small molecule
- Pirfenidone is active in cell cultures and several animal models of fibrosis
  - Including lung, liver, heart, and kidney
  - Active at clinically relevant exposures
  - ~ 40 peer reviewed publications
- Inhibits TGF-β and TNF-a

Pirfenidone: Mechanism of Action (Preclinical Studies)



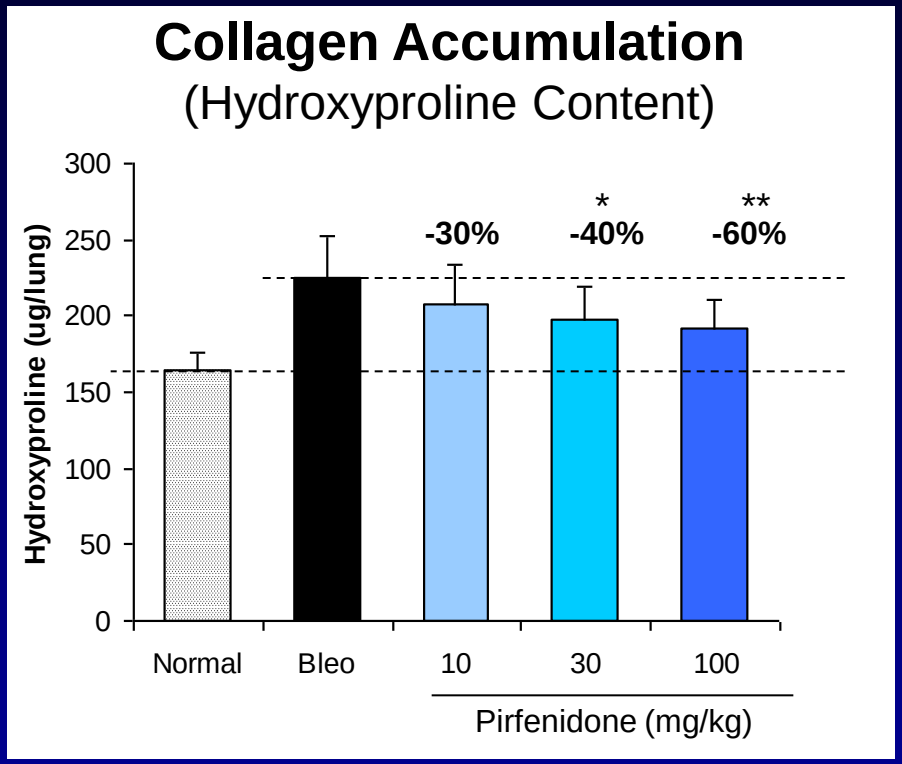
Effects on pulmonary fibrosis

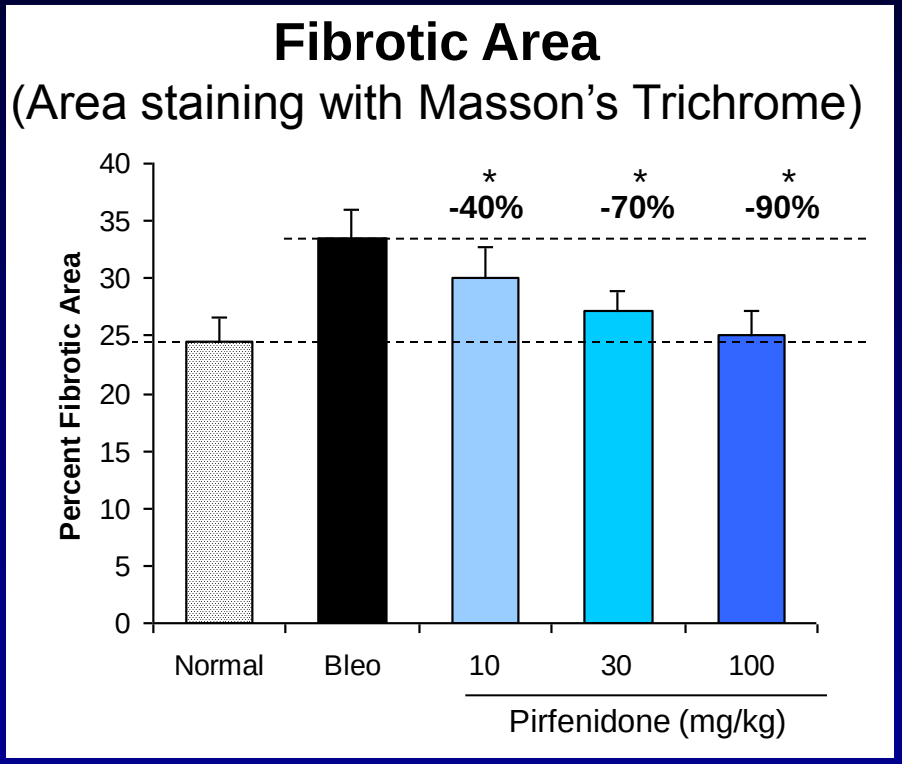
Delayed Pirfenidone Treatment Reduces Pulmonary Fibrosis *(Oku, Personal Communication)*



- **Delayed pirfenidone administration (Days 15 - 42)**
  - **Effect on an established fibrotic process**
  - **Inflammation had subsided at treatment initiation**
- **Parallel PK establishes that treatment effects are observed at clinically relevant exposures**

Delayed Pirfenidone Treatment Reduces Pulmonary Fibrosis *(Oku, personal communication)*





- **Pirfenidone treatment reduced progression of established bleomycin-induced fibrosis**
- **Effects were observed at clinically relevant exposures**

*P<0.05 or **P<0.01 for treated vs. untreated

Summary of Preclinical Data

- Pirfenidone is active in several animal models of fibrosis
  - **Including lung, liver, heart, and kidney**
  - **Reduced fibrosis and improved function**
  - **Active at clinically relevant exposures**

- The molecular target of pirfenidone is not known, however, strong evidence of anti-fibrotic activity exists
  - ***In vitro* and *in vivo* studies establish effects on final common pathways for fibrosis and inflammation**
  - **Pirfenidone modulates extracellular matrix deposition, production of cytokines and growth factors, and fibroblast proliferation**

Clinical Trials

Pirfenidone: The first approved IPF therapy

Pirfenidone (Pirespa®) was approved for IPF patients in Japan (October 2008).

Pirfenidone (Esbriet®) was approved for IPF patients in Europe (February 2011).

- Therapeutic indications: for mild- to moderate IPF in adults
- Pharmaceutical form: 267 mg hard capsules (oral administration)
- Recommended dose: 3 x 3 capsules per day after initial titration
- Should be initiated and supervised by a physician specialized in treatment of IPF

Pirfenidone Trials in IPF

0bservational / Japanese Phase II and III

- **Raghu et al., AJRCCM, 1999:**

– Observational study; n=54; 2 years duration; progr. disease; stabilisation observed;
major limitation: no control group

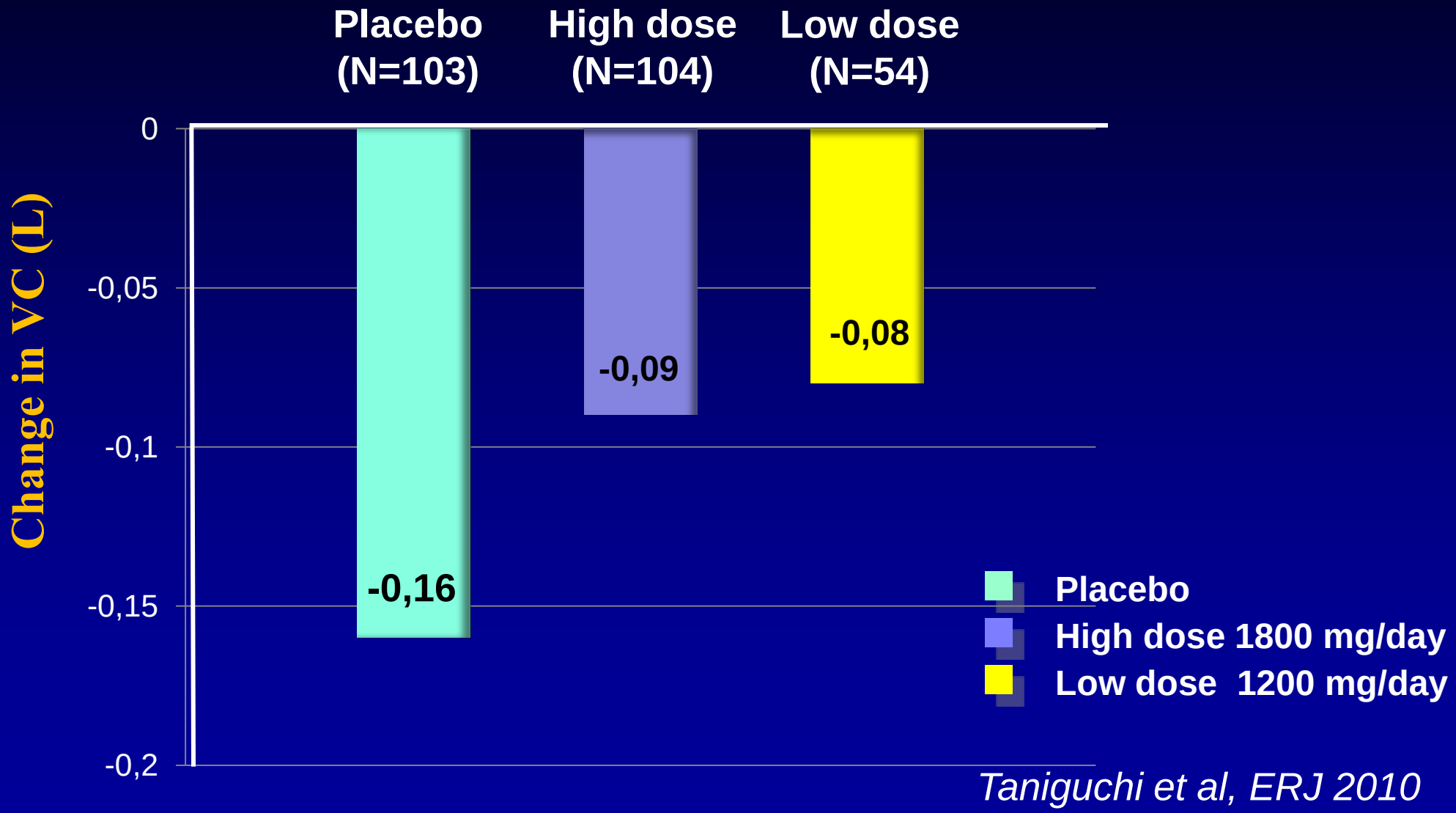
- **Azuma et al., AJRCCM, 2005:**

– RCT, Phase II, n=109, 1800 mg vs. Placebo 2:1;
– primary endpoint (minimal SpO2 with exercise) not met;
– Decline of FVC with pirfenidone significantly less compared to placebo
limitation: Premature study discontinuation due to five acute exacerbations in placebo arm versus zero in pirfenidone arm

- **Taniguchi et al., ERJ, 2010:**

– RCT, Phase III, n=267; 2:2:1 (1800mg:1200mg:Plac.)
– Significant effect on decline of FVC and on progression-free survival
limitation: Primary endpoint was changed before deblinding

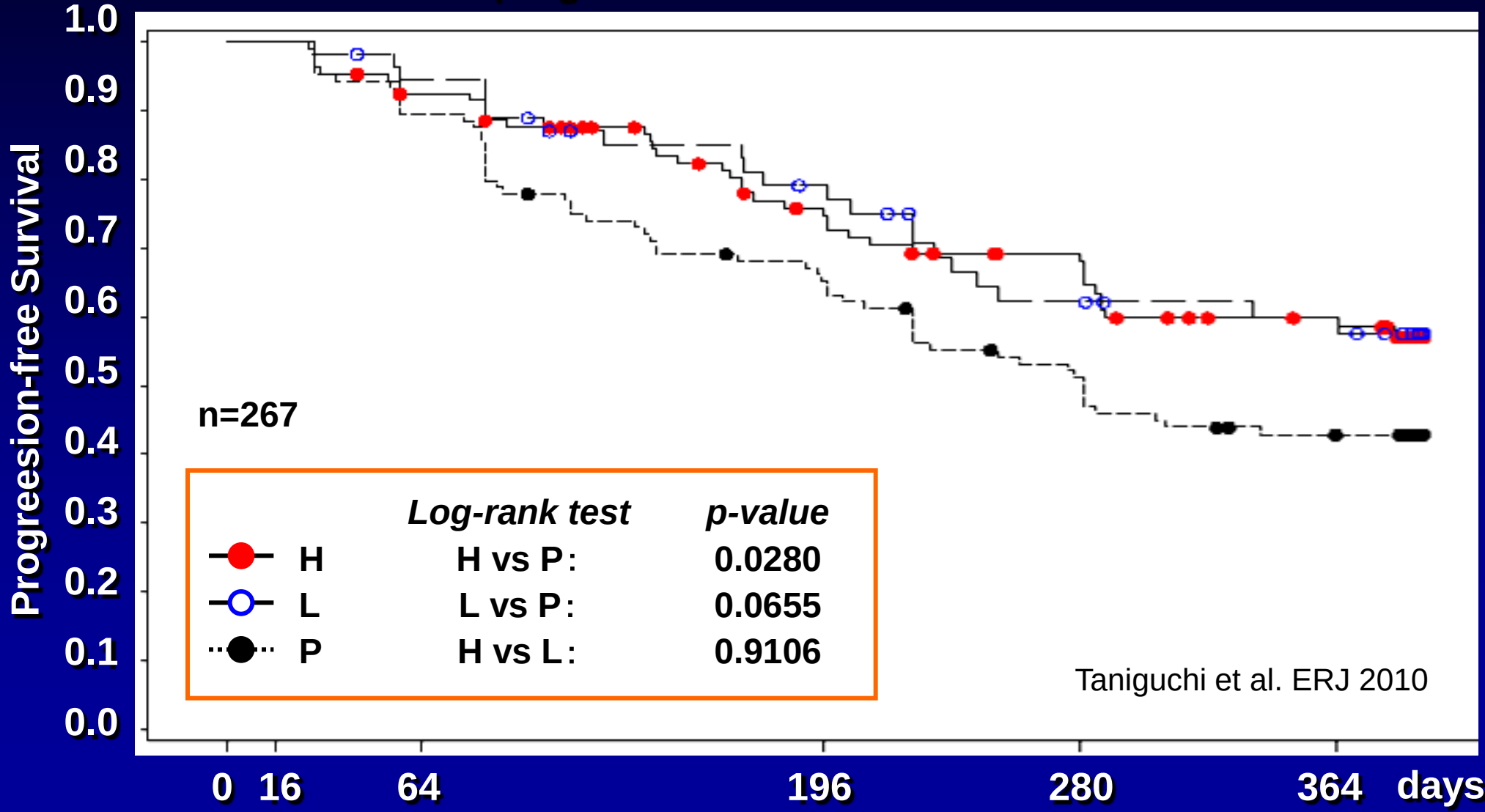
Pirfenidone in IPF: Phase III clinical trial in Japan
Change in VC (ΔVC) at week 52



Taniguchi et al, ERJ 2010

Pirfenidone in IPF: Phase III clinical trial in Japan
Progression-free Survival (52 weeks)

Definition of disease progression: death or more than 10% decrease in VC



Taniguchi et al. ERJ 2010

Pirfenidone in IPF: CAPACITY phase III trials

(Sponsor: Intermune)

- Two concurrent, nearly identical, multinational, RDBPC trials: 110 sites in 11 countries in Europe and North America
- Patients randomized to treatment with oral pirfenidone (TID) or matched placebo for a minimum of 72 weeks

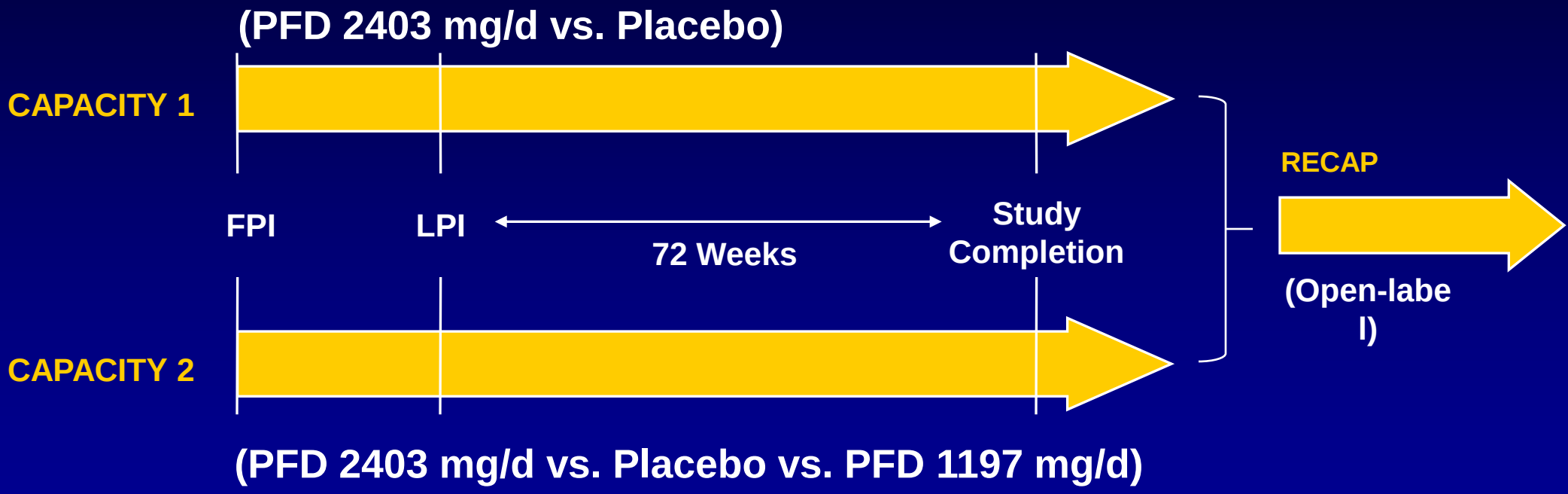
CAPACITY 1 (N = 344): PFD 2403 mg/d vs. Placebo (1:1)

CAPACITY 2 (N = 435): PFD 2403 mg/d vs. Placebo vs. PFD 1197 mg/d (2:2:1)

- Eligibility required a confident diagnosis of IPF
  - Baseline % predicted FVC ≥ 50% and DL_{co} ≥ 35%
- Primary Endpoint: Absolute change in % predicted FVC from baseline to Week 72 (ITT analysis, Rank ANCOVA)

Noble PW et al, Lancet 2011; 377: 1760

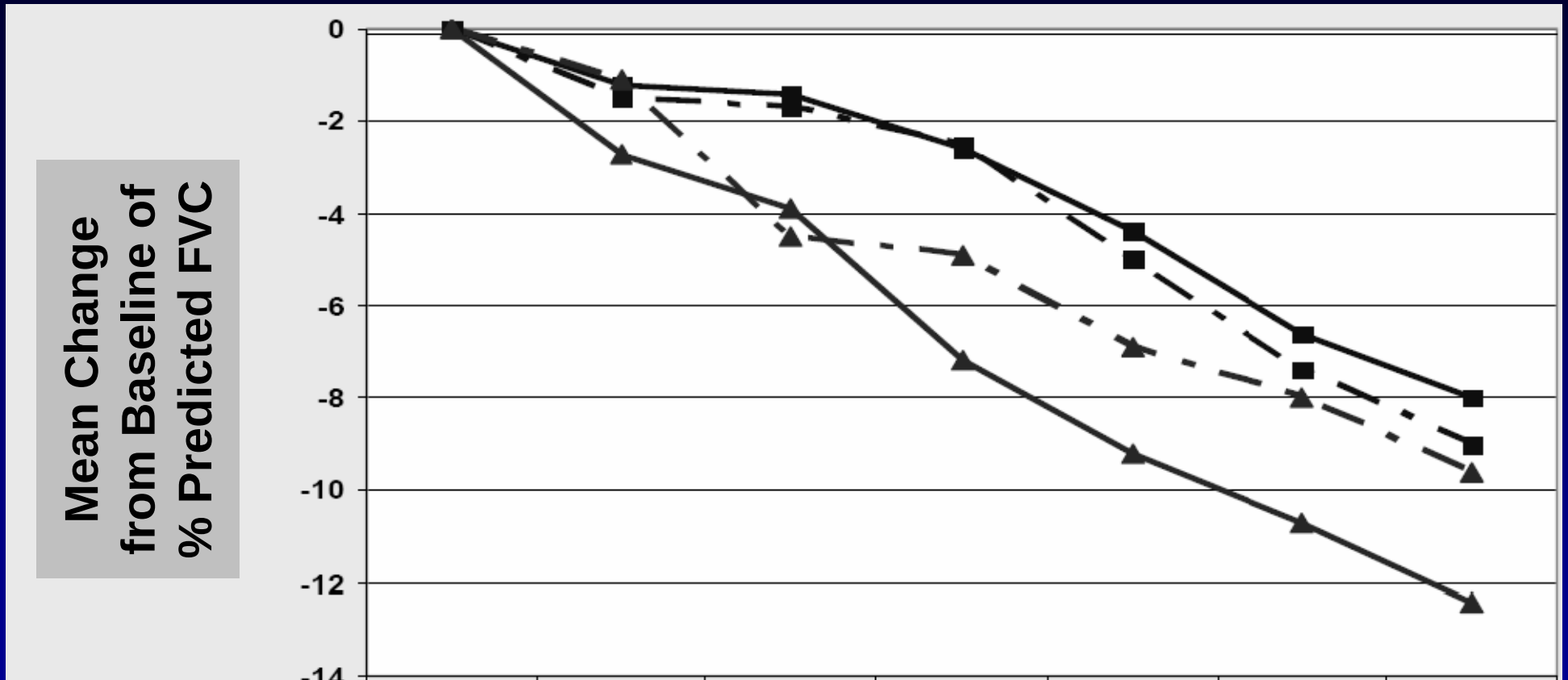
CAPACITY Trials: Pirfenidone in IPF



FPI: First patient in; LPI: Last patient in

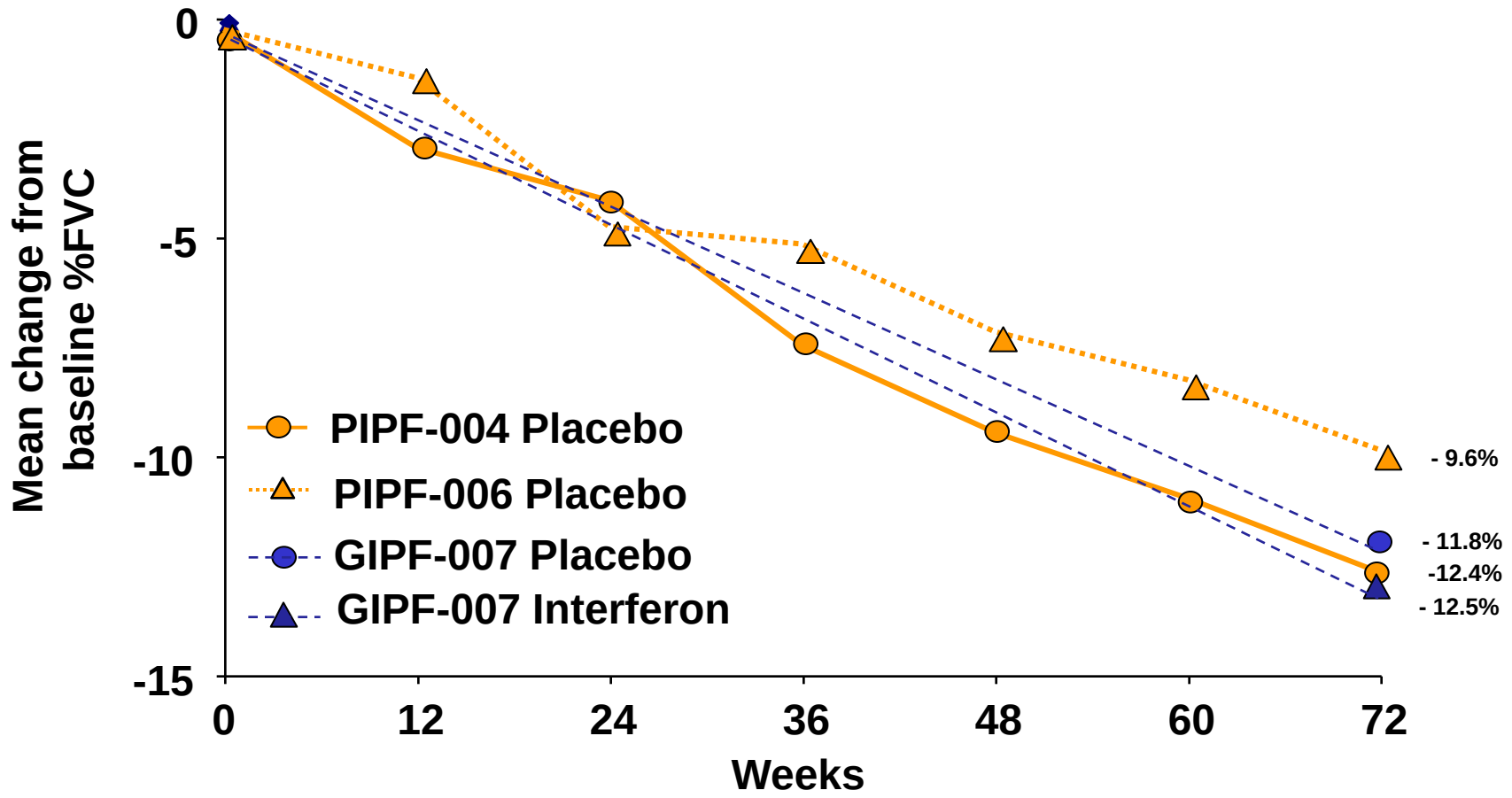
Pirfenidone in IPF: CAPACITY 1 and 2 Trials

Change in % Predicted FVC



	Baseline	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72
pirfenidone-004	74.5	-1.2	-1.4	-2.6	-4.4	-6.6	-8
placebo-004	76.2	-2.7	-3.9	-7.2	-9.2	-10.7	-12.4
pirfenidone-006	74.9	-1.5	-1.7	-2.5	-5	-7.4	-9
placebo-006	73.1	-1.1	-4.5	-4.9	-6.9	-8	-9.6

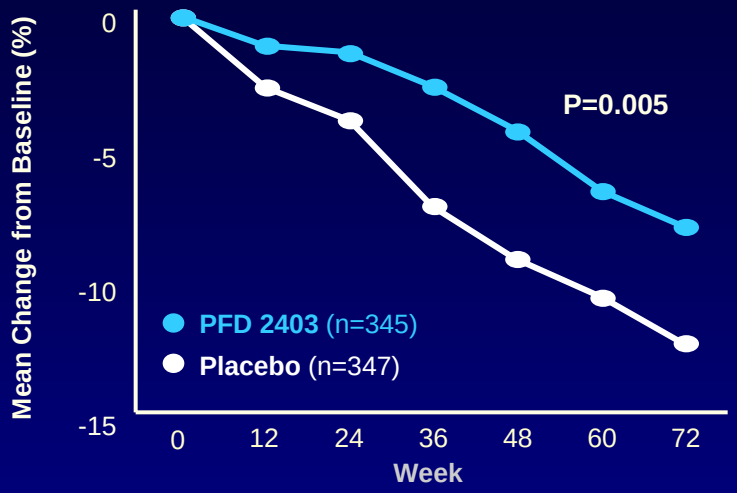
Change in % Predicted FVC Over Time PIPF-004 and PIPF-006 Placebo vs. INSPIRE (GIPF-007)



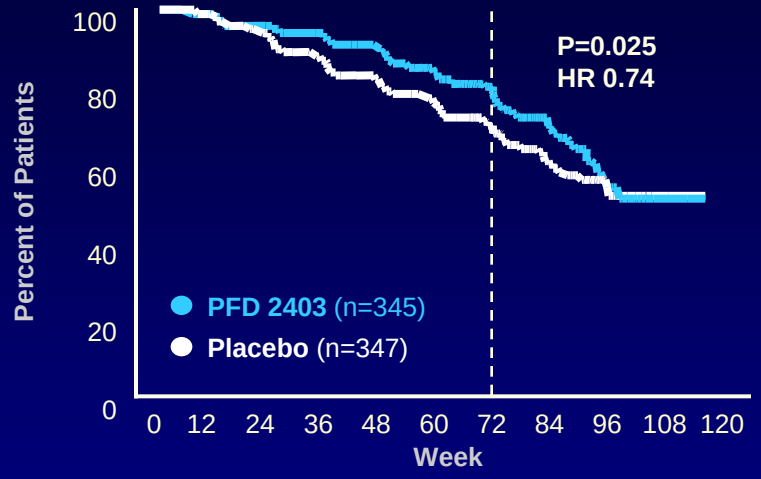
Data on file. InterMune, Inc. 2010.

CAPACITY: Pooled Efficacy Results

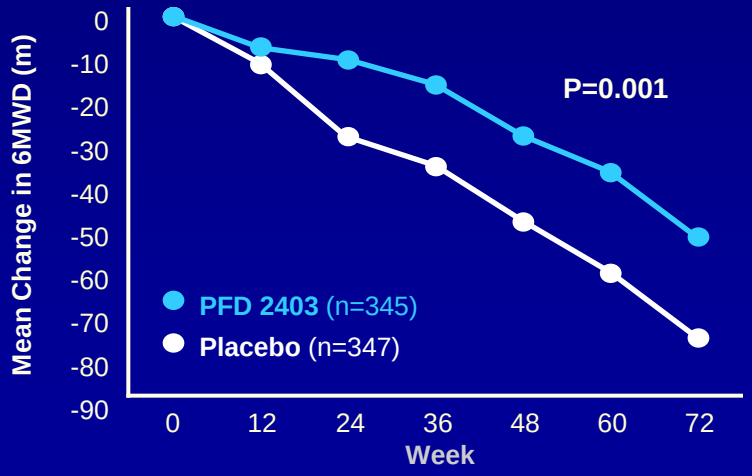
Mean Change in % Predicted FVC



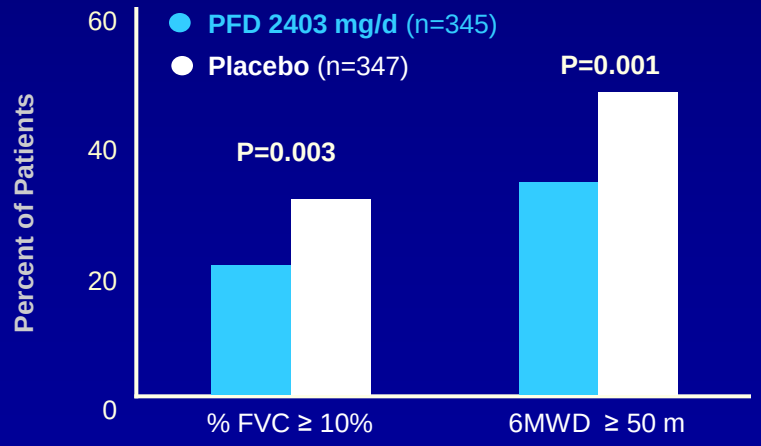
Progression-free Survival Time



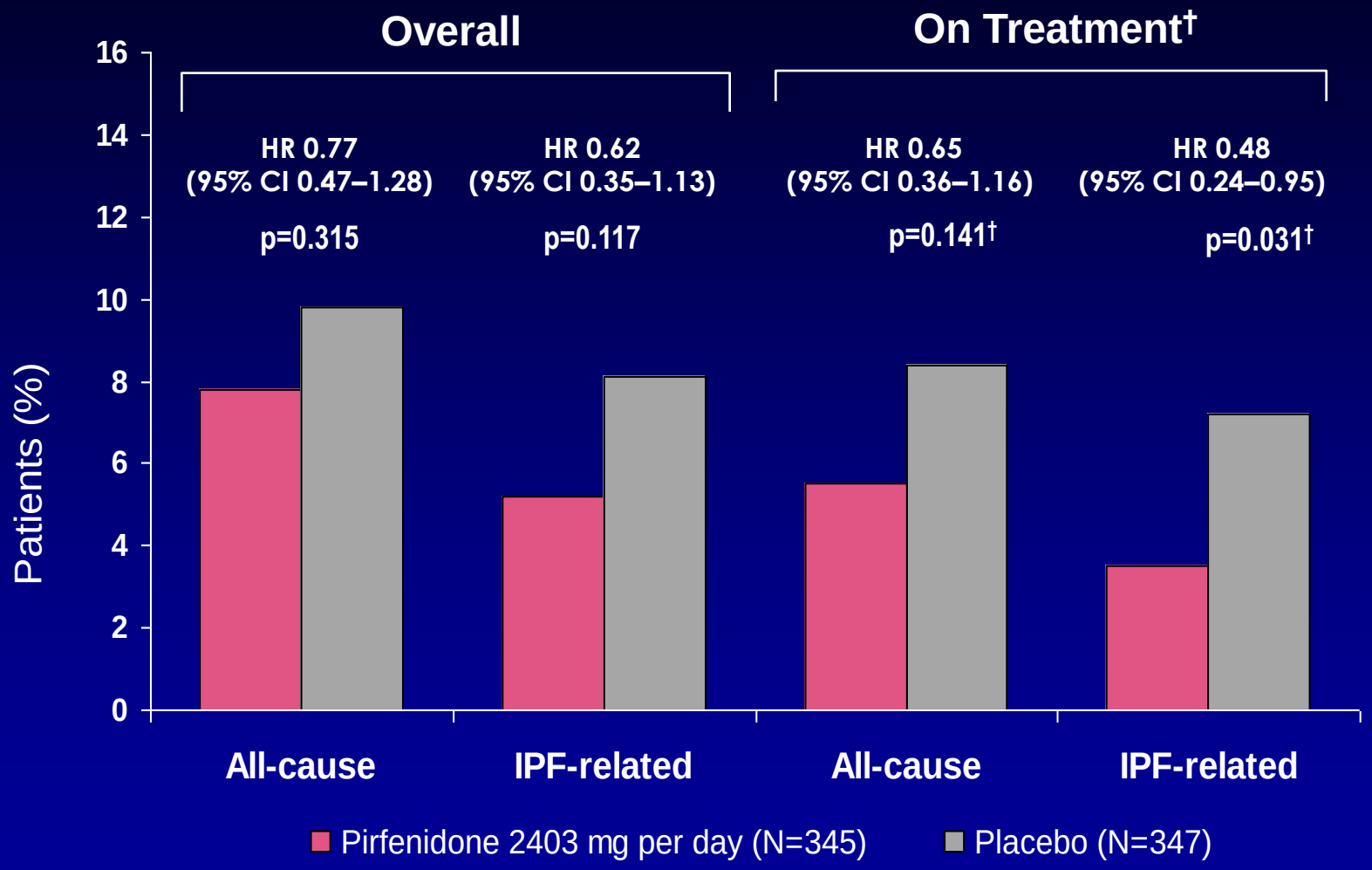
Mean Change in 6MWT Distance



Categorical Decline in FVC and 6MWD



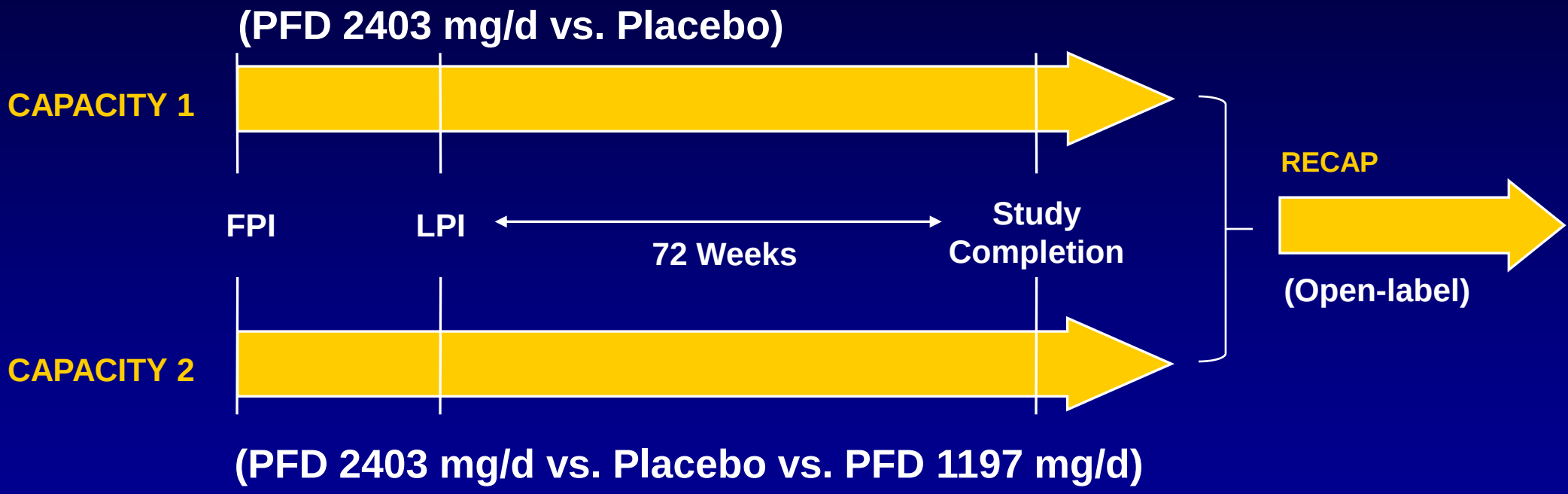
Mortality Analysis*



†Occurring between randomization and 28 days after the last dose of study drug

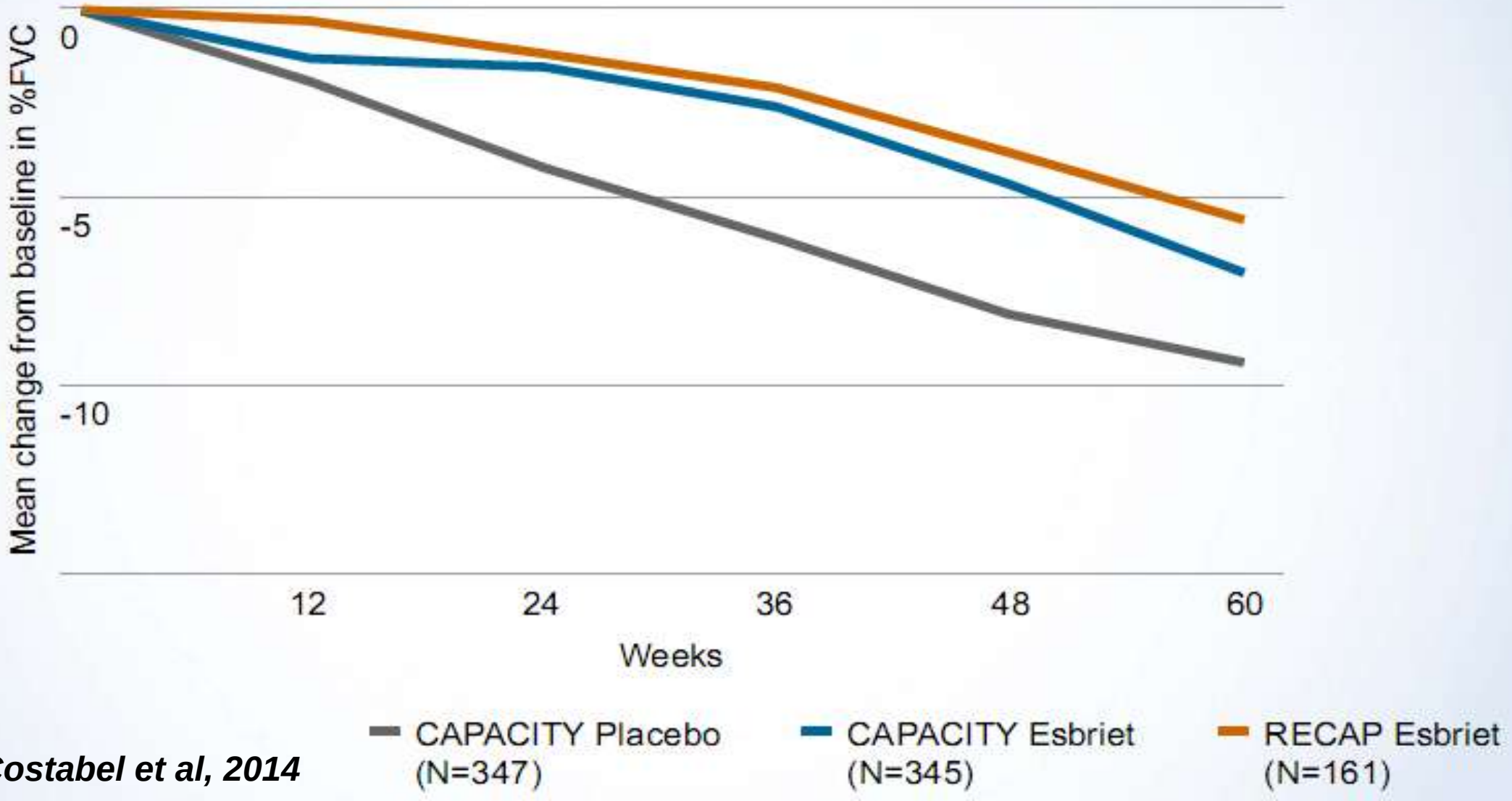
* Assessed by the investigator – Exploratory pooled analysis

CAPACITY Trials: Pirfenidone in IPF



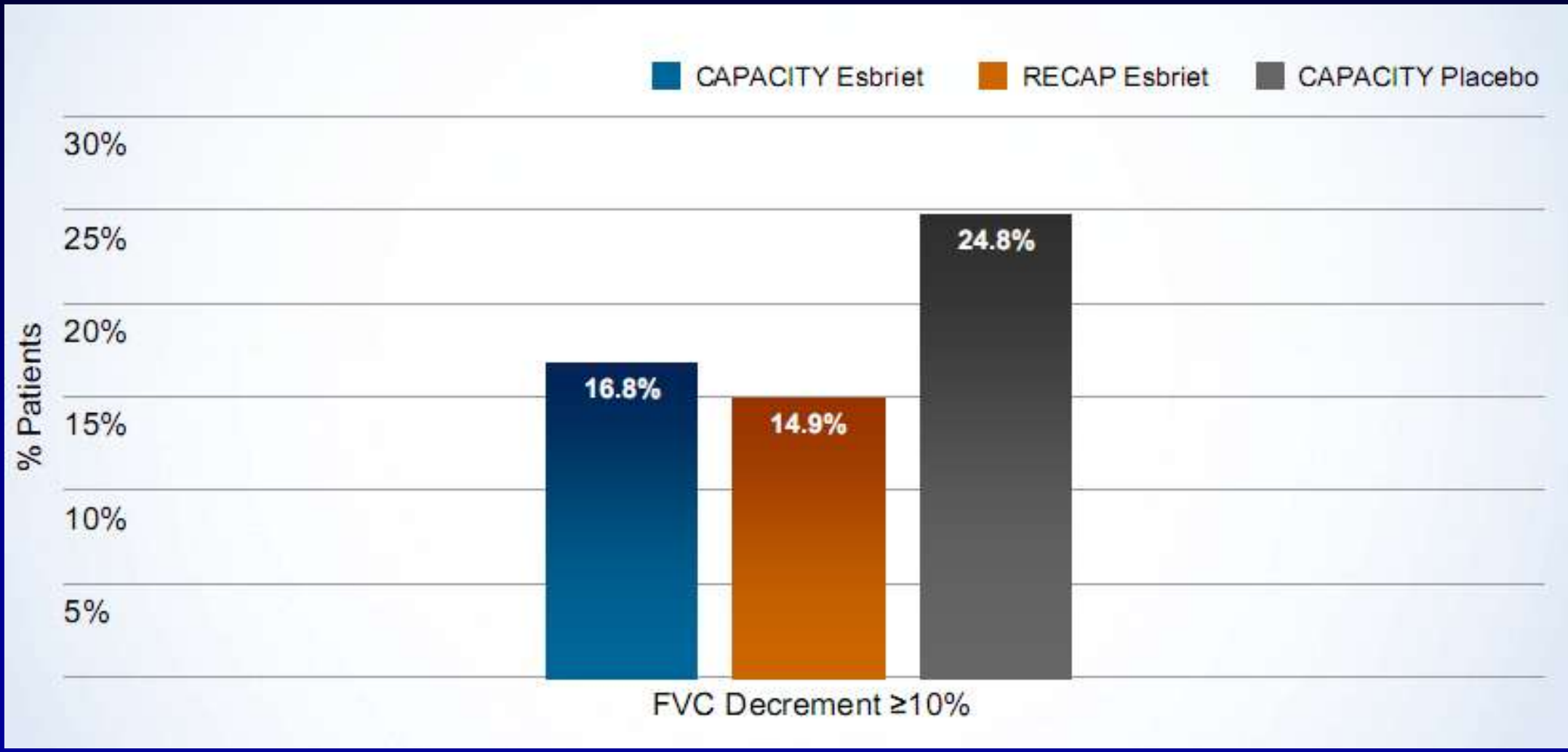
FPI: First patient in; LPI: Last patient in

FVC changes in CAPACITY and RECAP

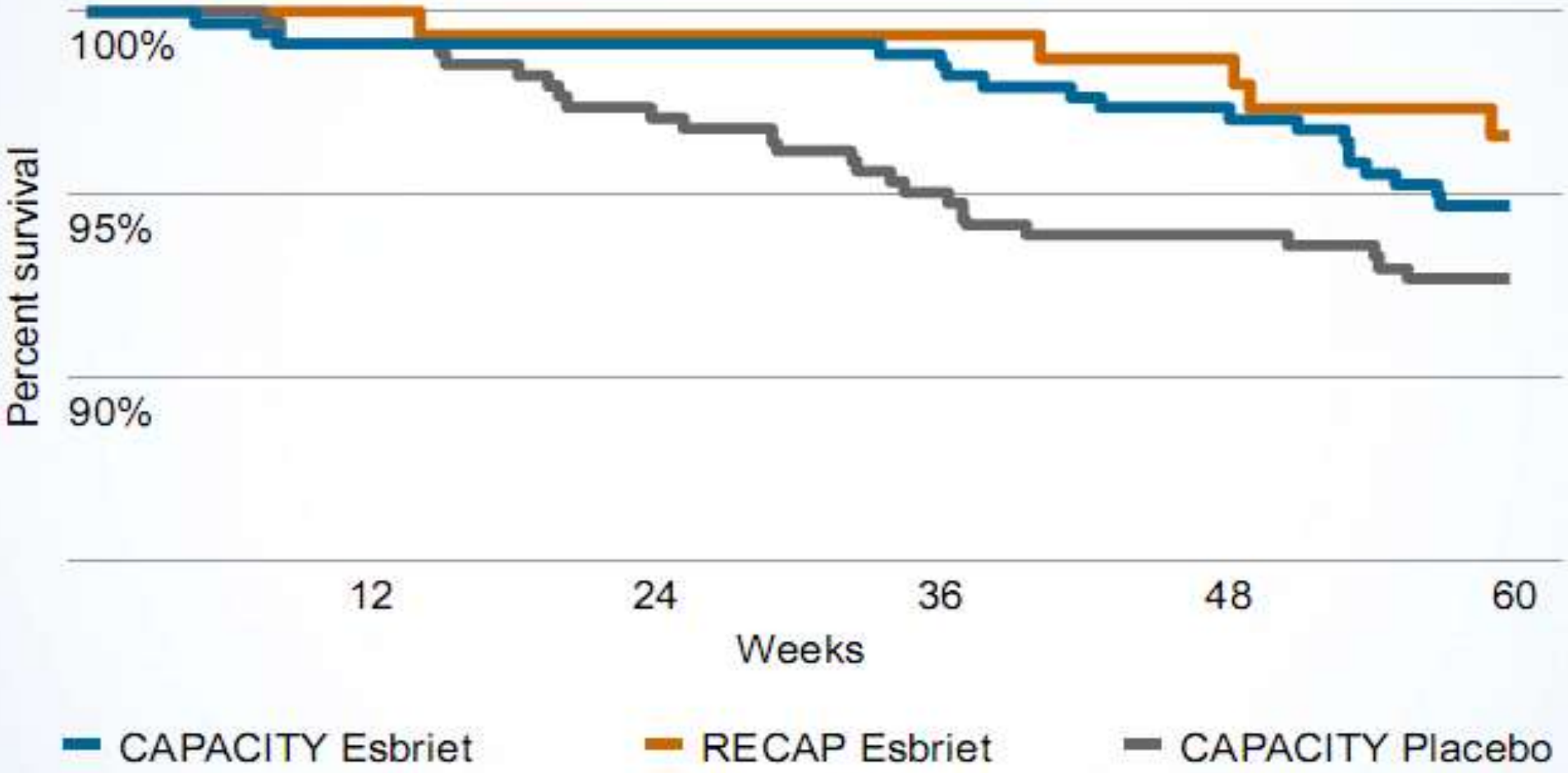


Costabel et al, 2014

FVC decrease of ≥ 10% at week 60



Overall survival in CAPACITY and RECAP



Costabel et al, 2014

Adverse events occuring in >10% of patients in CAPACITY

	Pirfenidone (n=345) %	Placebo (n=347) %
Nausea	36	17
Rash	32	12
Dyspepsia	19	7
Dizziness	18	10
Vomiting	14	4
Photosensitivity	12	2
Anorexia	11	4

Noble et al, Lancet 2011

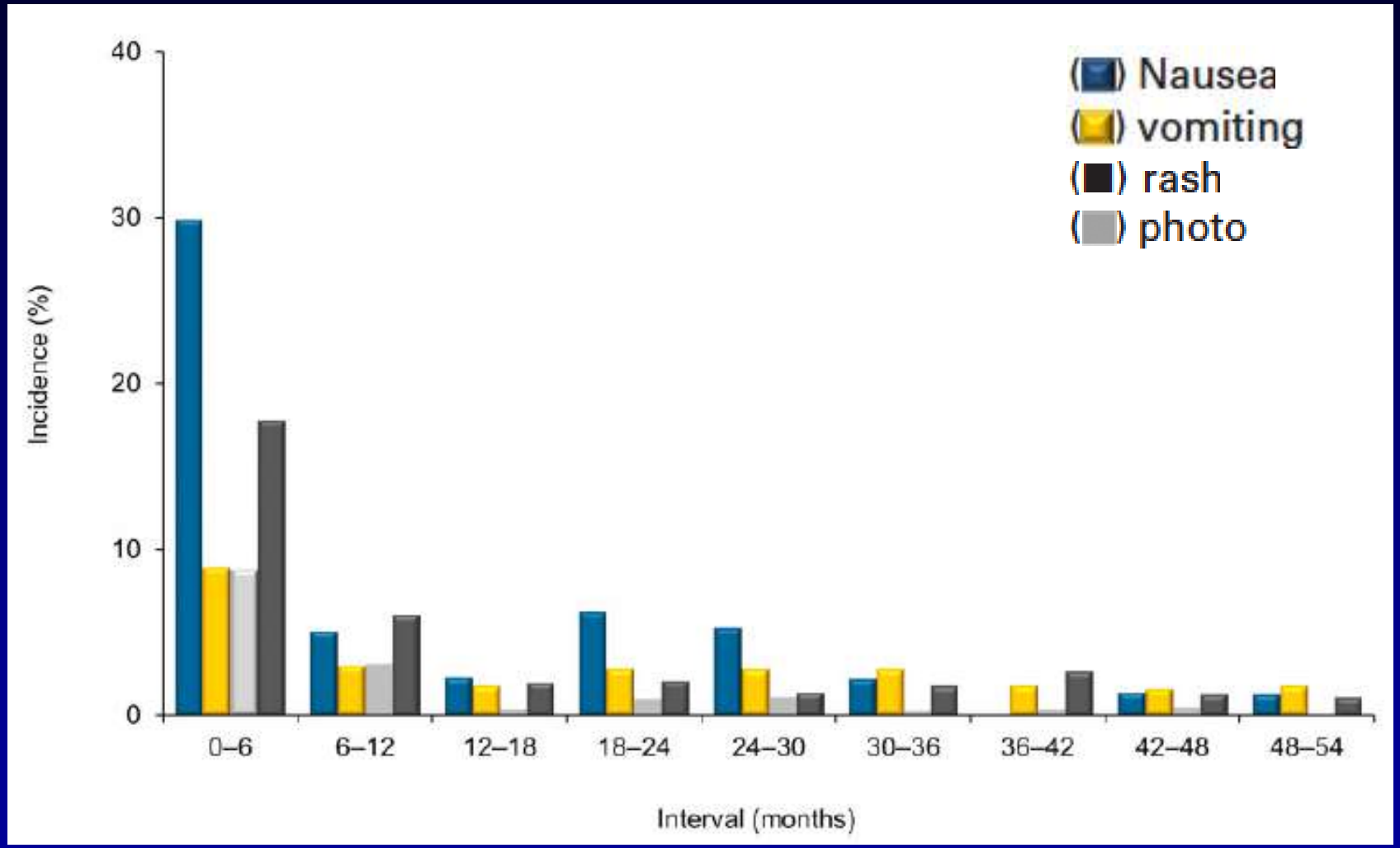
Treatment-emergent adverse events* in pirfenidone open-label trials vs CAPACITY trials

	Pirfenidone open label	CAPACITY	
	Integrated population (n = 789)	Pirfenidone 2403 mg/day (n = 345)	Placebo (n = 347)
Median duration of exposure, years	2.6	1.4	1.4
Any TEAE (%)	99.7	98.6	97.7
Any TE SAE (%)	53.0	32.8	31.4
Any TEAE leading to tx discontinuation (%)	35.1	14.8	8.6

* Occurring after the first dose and within 28 days of the last dose of study treatment. TEAE, treatment-emergent adverse event; TE SAE, treatment-emergent serious adverse event.

Valeyre et al , Respirology 2014

Incidence of new-onset treatment-emergent AEs by 6-month intervals in the integrated population



Valeyre et al , Respirology 2014

The ASCEND Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

NEJM 2014;370:2083

ASCEND: Study Design

- Randomized, double-blind, placebo-controlled trial
- Eligible patients randomized (1:1) to treatment with pirfenidone 2403 mg/d (n=278) or matched placebo (n= 277) for 52 wk
- Centralized review of HRCT, SLB, spirometry and deaths instituted to confirm eligibility and ensure high-quality efficacy assessments
- 127 sites in 9 countries (U.S., Australia, Brazil, Croatia, Israel, Mexico, New Zealand, Peru, and Singapore)

King et al, NEJM 2014

ASCEND Trial

Inclusion criteria

ASCEND:

- FVC ≥ 50% and ≤ 90%
- DLco ≥ 30% and ≤ 90%
- FEV1/FVC ratio ≥ 0.80
- Time since IPF diagnosis ≥ 6 mo

CAPACITY:

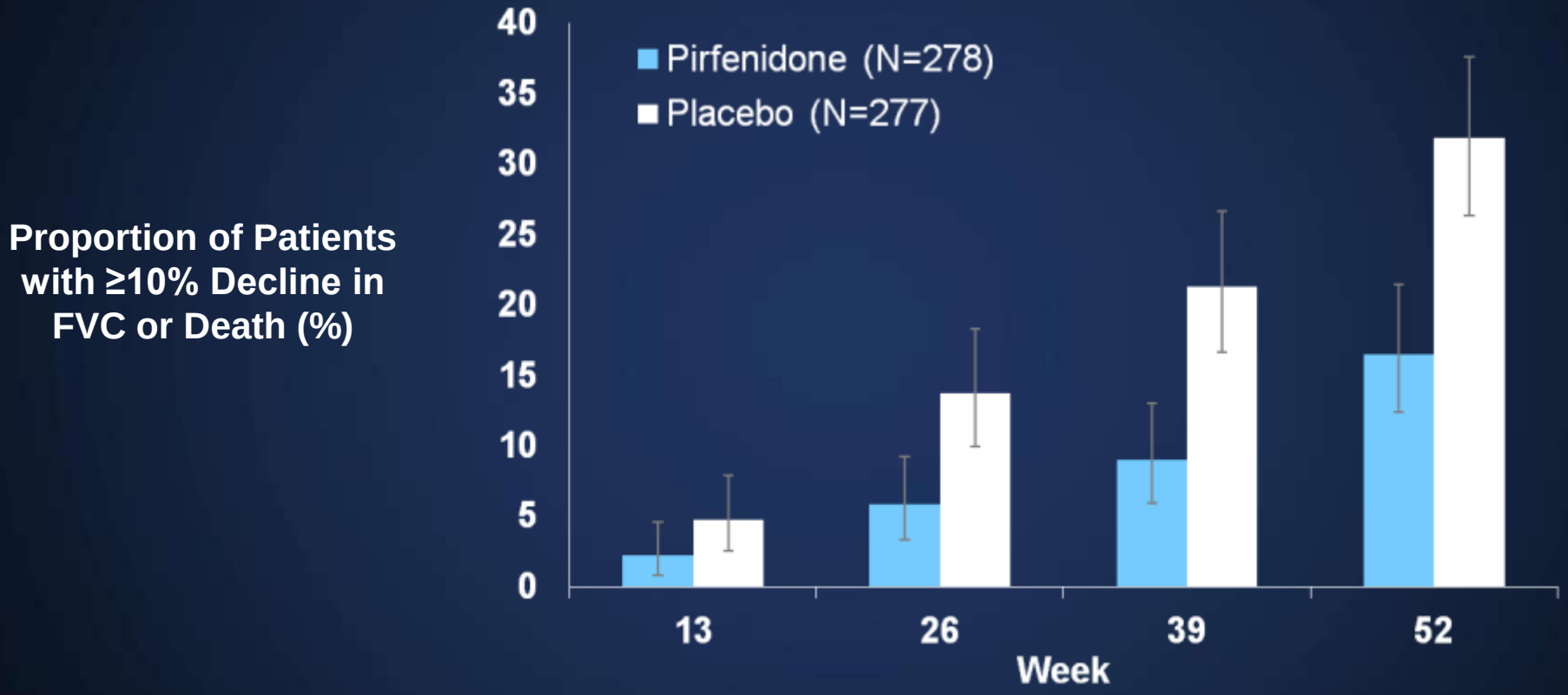
- FVC ≥ 50%
- DLco ≥ 35%
- ratio ≥ 0.70
- ≥ 1 year

⟹ Enrichment of more rapid progressors

ASCEND Study Design
Primary Endpoint

- Percent of pred. 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

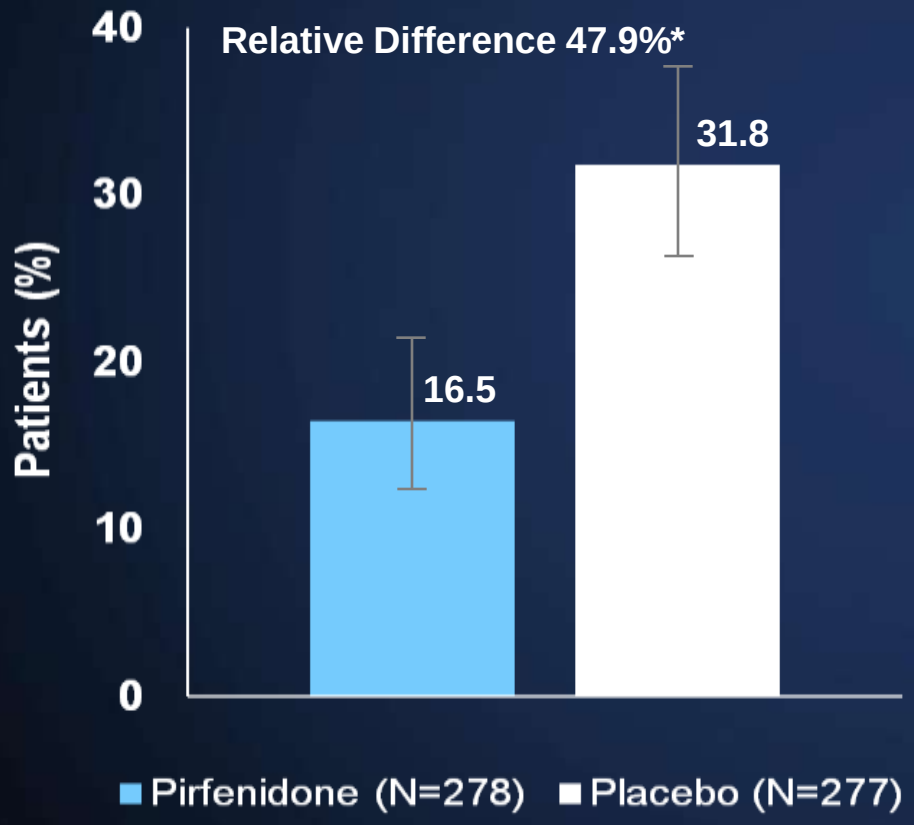
Primary Efficacy Analysis: Treatment with pirfenidone resulted in a significant between-group difference in the rank ANCOVA analysis (P<0.000001)



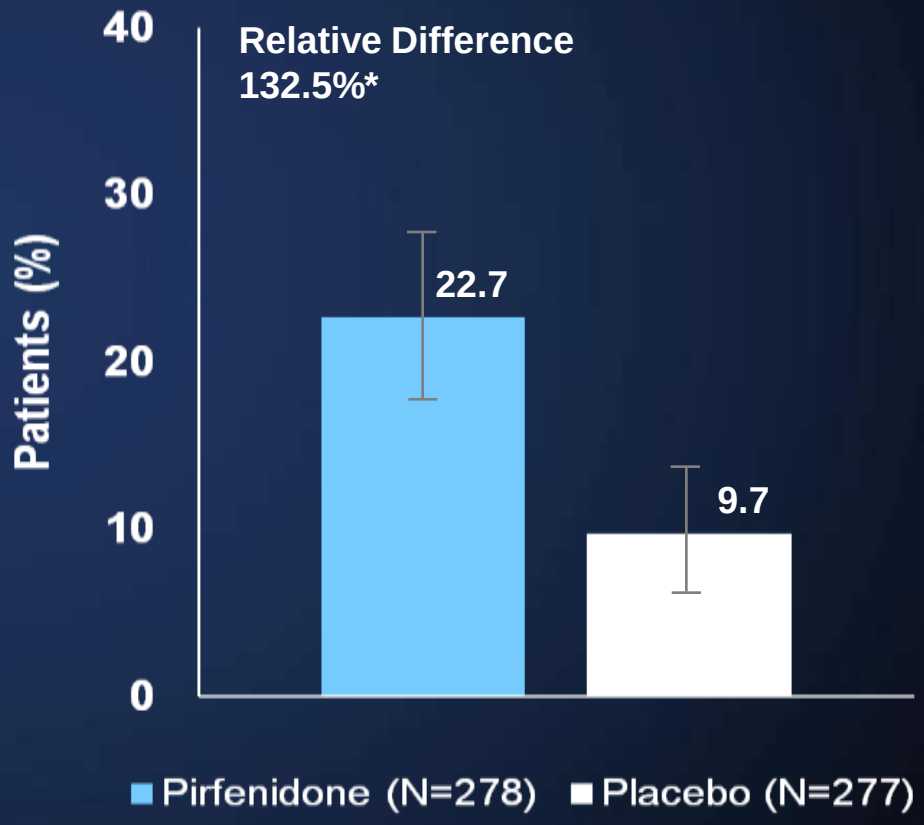
Absolute Difference	2.5%	7.9%	12.3%	15.3%
Relative Difference	54.0%	58.0%	57.8%	47.9%
Rank ANCOVA p-value	<0.000001	<0.000001	0.000002	<0.000001

Primary Efficacy Analysis: %FVC Change at Week 52

%FVC Decline ≥10% or Death



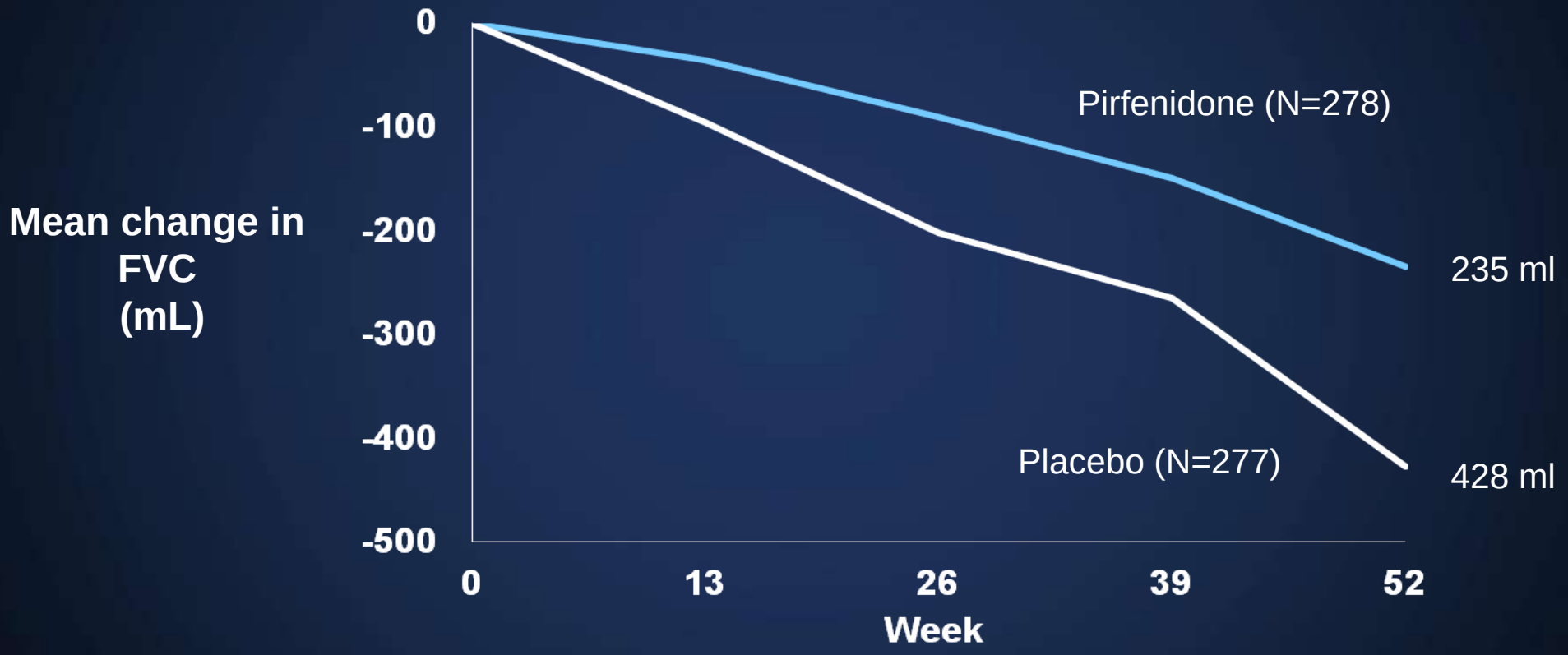
No Decline in %FVC



* Rank ANCOVA p-value <0.000001

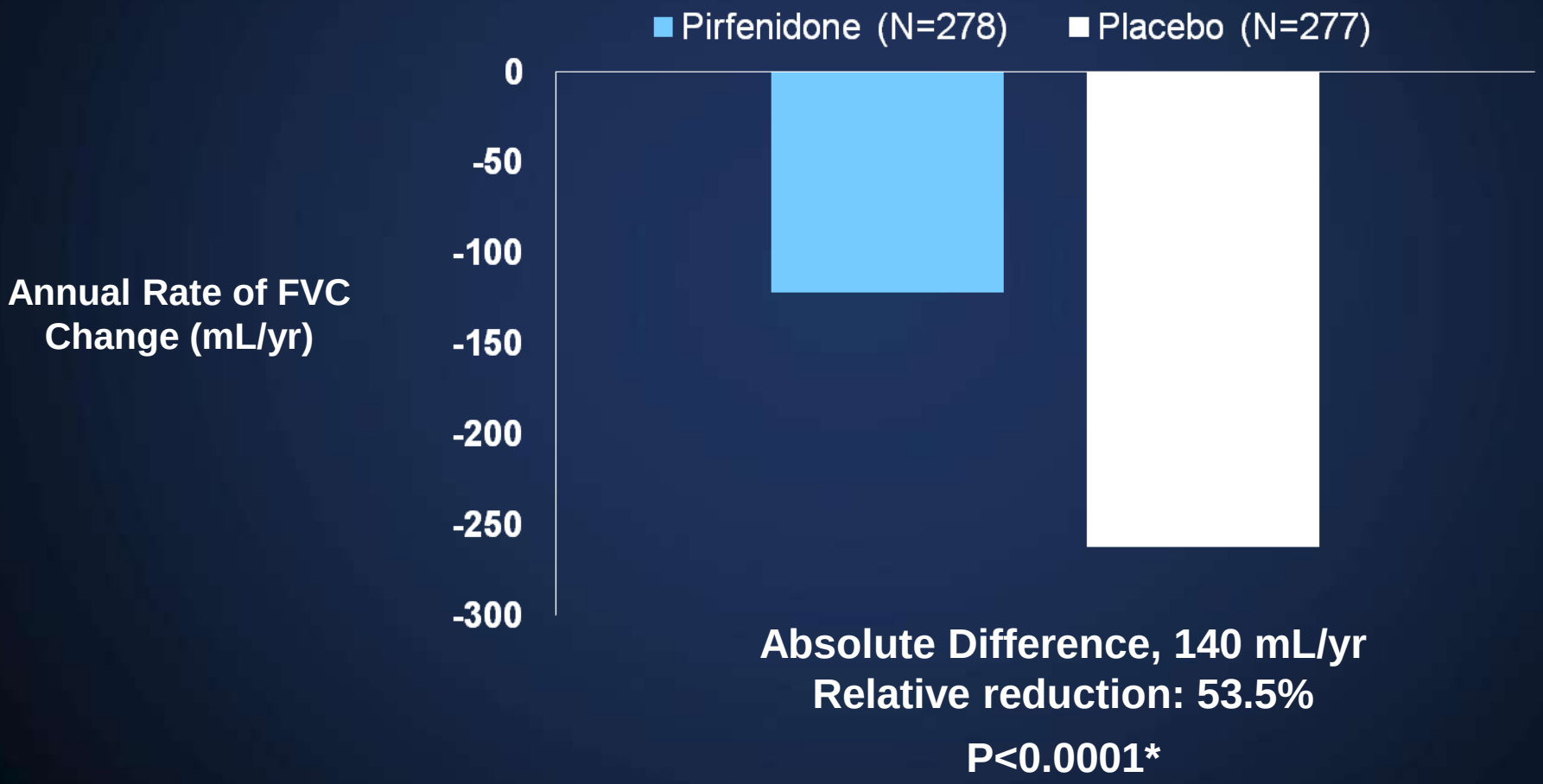
Supportive Analysis of the Primary Endpoint:

Treatment group difference at Week 52: a 45% relative reduction in the mean change in FVC



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

Supportive Analysis of the primary endpoint: Annual rate of FVC decline at week 52 favored Pirfenidone (Linear Slope Analysis)



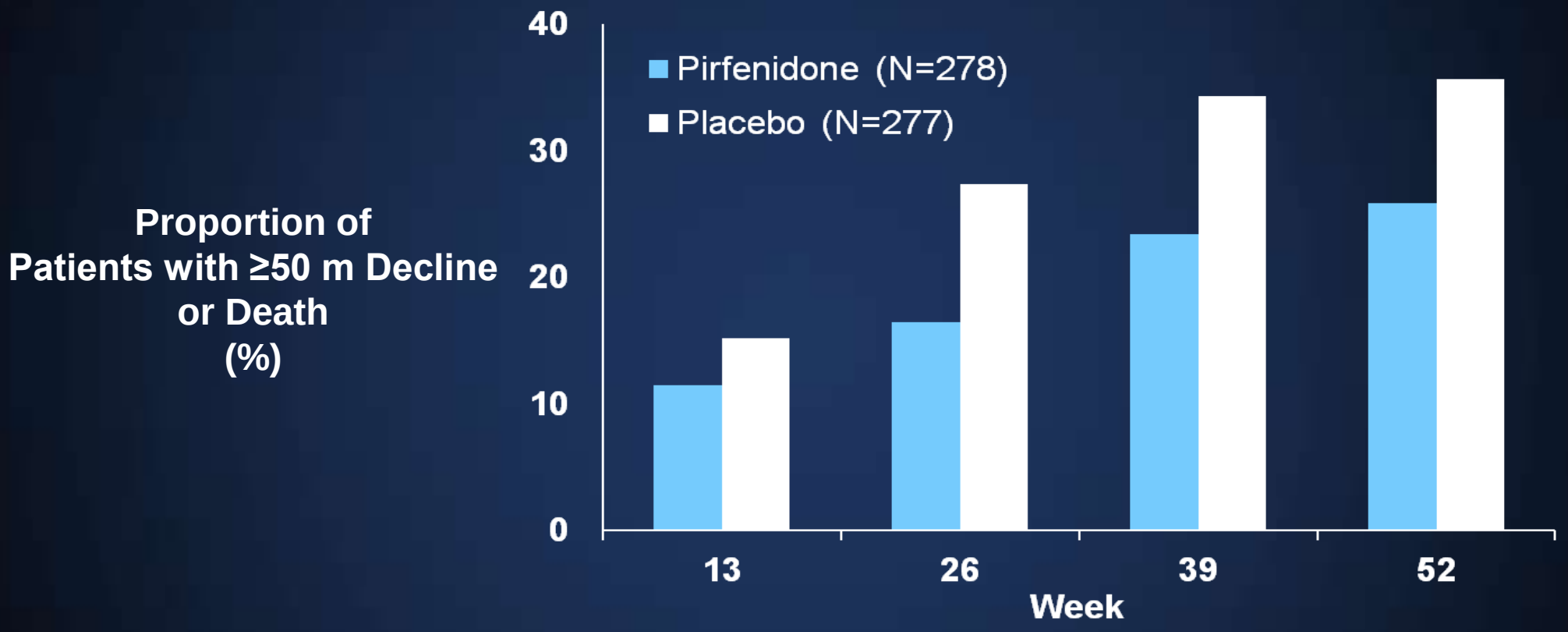
* Linear slope analysis: Mixed model with linear time effect adjusted for age, height, and sex

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

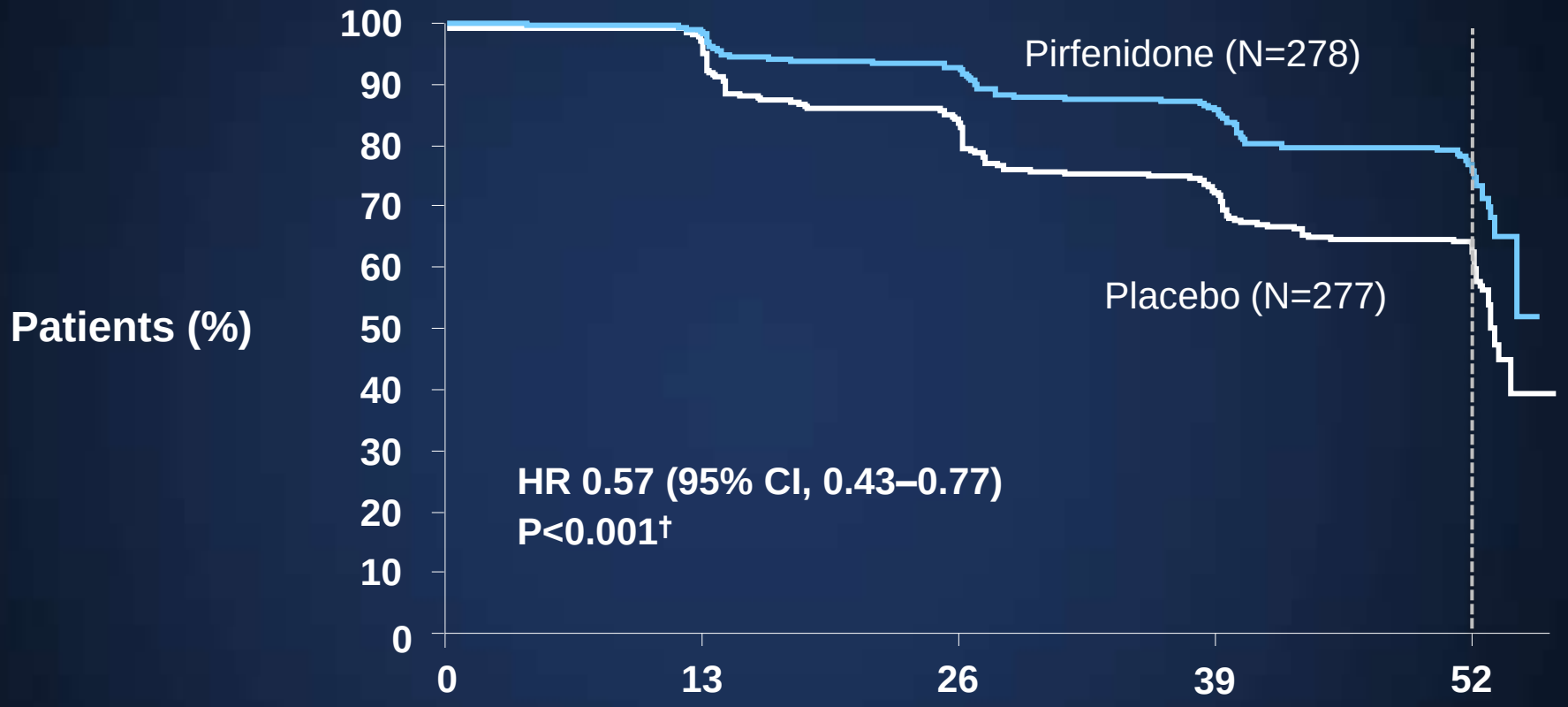
6-Minute Walk Distance: Significant between-group difference in the change from baseline to week 52



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

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



Patients at Risk:

Pirfenidone	276	262	243	219	144
Placebo	273	269	225	192	113

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

ASCEND Study Design
Additional Secondary Endpoints

- Dyspnea change from Baseline to Week 52 (UCSD SOBQ score)
- All-cause mortality (ASCEND alone and pooled with CAPACITY)
- Treatment emergent IPF-related mortality* (ASCEND alone and pooled with CAPACITY)

* Deaths related to IPF occurring between baseline and 28 days of the last dose of study drug; cause of death assessed in a blinded fashion by an independent mortality assessment committee in the ASCEND study and clinical investigators in the CAPACITY studies

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

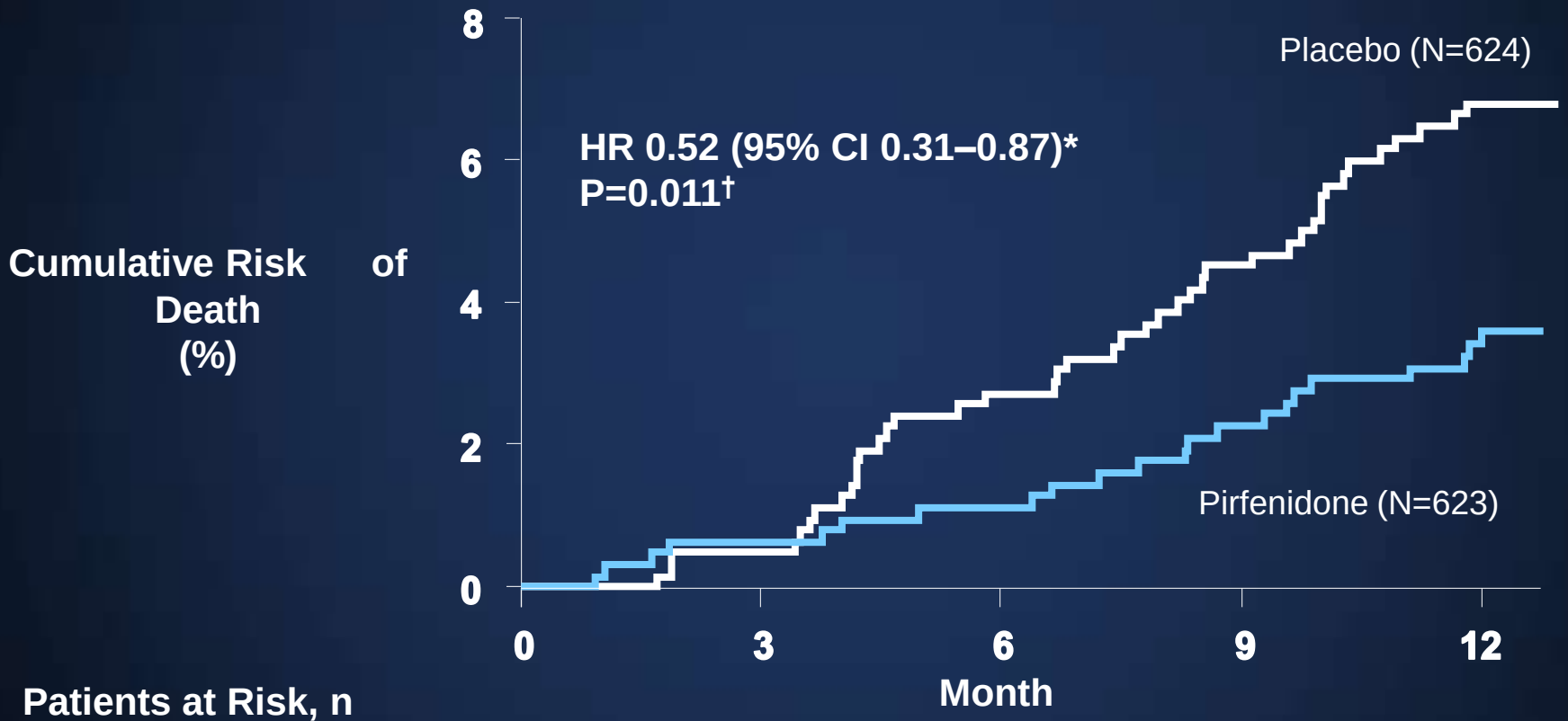
Patients, n (%)	Pirfenidone	Placebo	HR (95% CI)‡	P-value§
ASCEND* (N=555)	11 (4.0%)	20 (7.2%)	0.55 (0.26–1.15)	0.105
CAPACITY† (N=692)	11 (3.2%)	22 (6.3%)	0.49 (0.24–1.01)	0.047
Pooled Population* (N=1247)	**22 (3.5%)**	**42 (6.7%)**	**0.52 (0.31–0.87)**	**0.011**

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

Pooled All-cause Mortality (Week 52):

Treatment group curves diverge early and continue separating throughout the study period



Patients at Risk, n					
Pirfenidone	623	618	609	596	509
Placebo	624	619	603	586	490

* Cox proportional hazards model
† Log-rank test

Pooled ASCEND & CAPACITY (Week 52):

Treatment Emergent IPF-related Mortality

Pirfenidone reduced risk of death from IPF by 68%

Patients, n (%)	Pirfenidone	Placebo	HR (95% CI)‡	P-value§
ASCEND* (N=555)	3 (1.1%)	7 (2.5%)	0.44 (0.11–1.72)	0.226
CAPACITY† (N=692)	4 (1.2%)	15 (4.3%)	0.27 (0.09–0.81)	0.012
Pooled Population* (N=1247)	**7 (1.1%)**	**22 (3.5%)**	**0.32 (0.14–0.76)**	**0.006**

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

ASCEND Study: Summary

- Primary efficacy endpoint of FVC change achieved ($p<0.000001$) with clinically meaningful effect size (~50% relative difference)

- Both key secondary endpoints of 6MWD and PFS achieved

- Significant effect on all cause 1 year mortality (HR 0.52) in pooled analysis of ASCEND and CAPACITY-1 and -2

- Conclusion: Treatment with pirfenidone reduces the progression of IPF

Pirfenidone in Real Life

DMW
Deutsche
Medizinische Wochenschrift

138. Jahrgang | www.thieme-connect.de/ejournals | www.thieme.de/dmw 11 | 2013

Klinische Erfahrungen mit Pirfenidon in der Therapie der idiopathischen Lungenfibrose

Clinical experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis

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Institut [1] Abteilung Pneumologie-Allergologie, Ruhrlandklinik, Universitätsklinikum Essen, Universität Duisburg-Essen

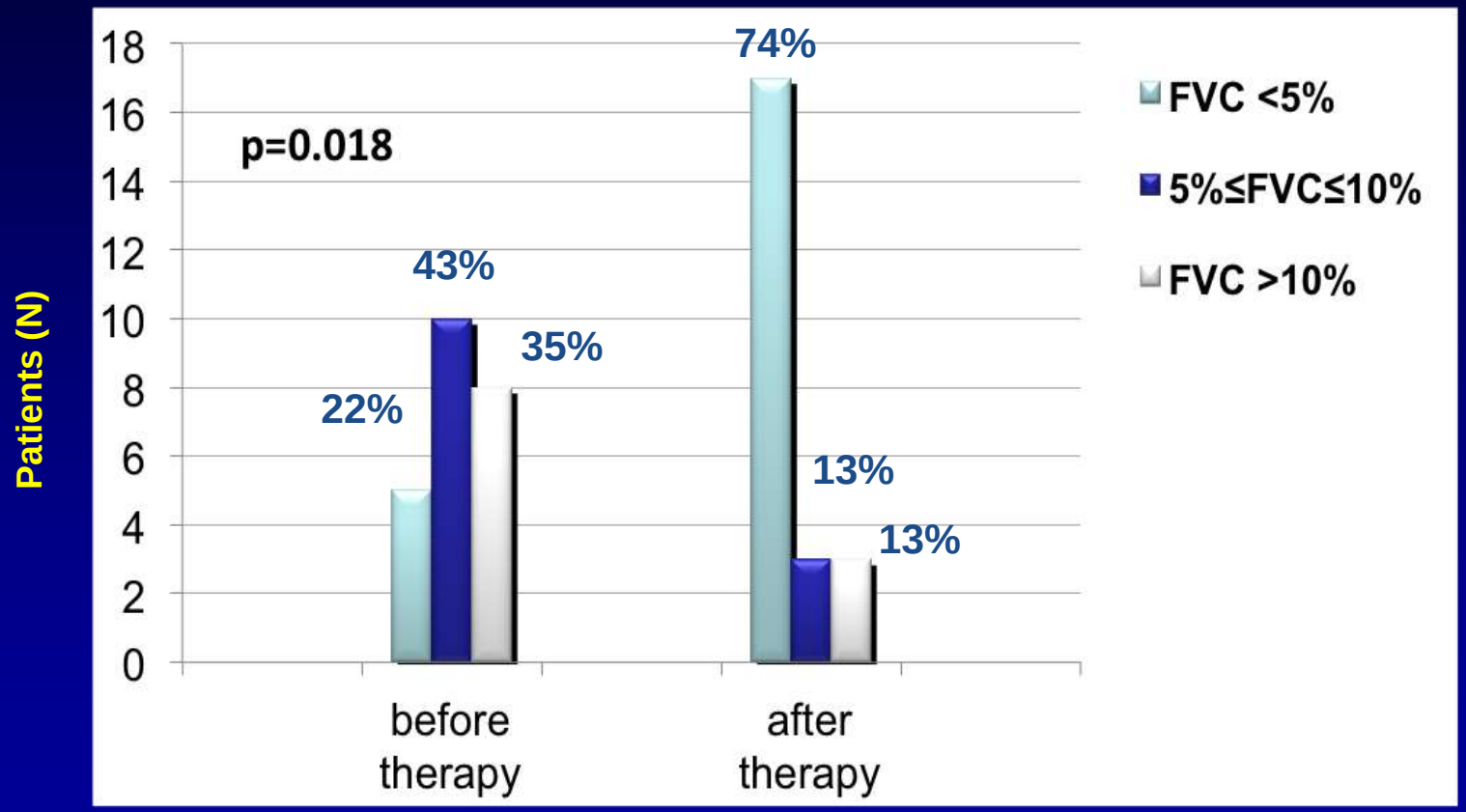
Course of Disease under Pirfenidone Treatment

Number of Patients (n=45)	
Follow-up (weeks)	60 (7-321)*
Duration of treatment (weeks)	48 (3-321)*
Stable, n (%)	28/40** (70)
Progress, n (%)	12/40** (30) ¶
Decrease in FVC, ml, 6 months before treatment	307 ± 271 (8% pred)
Decrease in FVC, ml, 12 months with treatment	132 ± 36 (3% pred)

* Average (range)
** 3 patients with follow-up < 3 months (not evaluable)
¶ 10 out of 12 patients experinced an acute exacerbation

Bonella F et al. DMW 2013;138: 518-23

Categorical change of vital capacity 6 months before and 6 months after treatment



Bonella et al, DMW 2013

Summary

Safety and Tolerance

- Side effeadjustmentcts: 60%
- Dose : 18%

Discontinuation

- Total: 33%
- Due to progress: 20%
- Due to side effects: 13%

Combination Therapy

- Pirfenidone was frequently combined with steroids and NAC

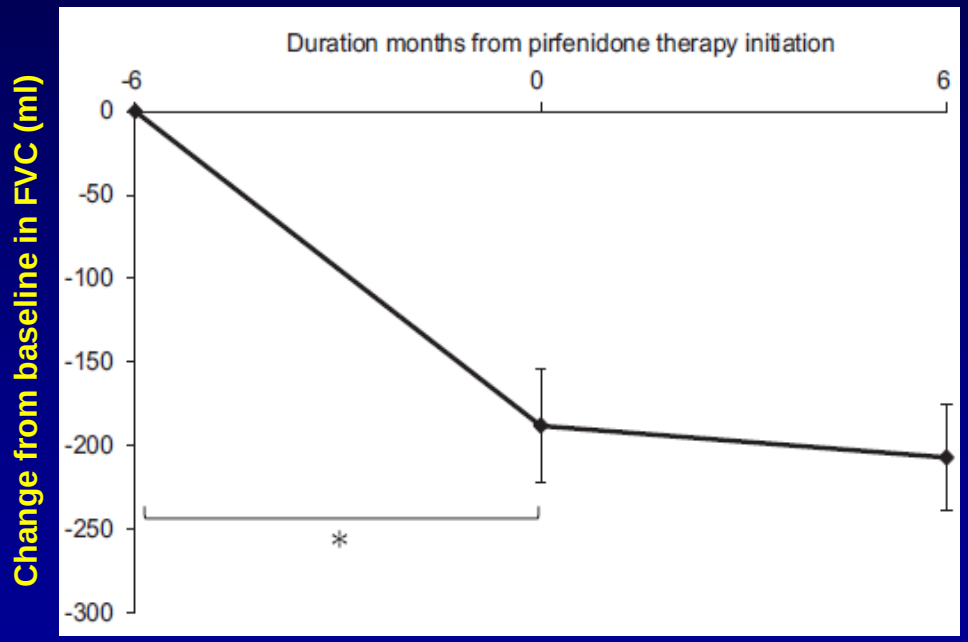
Course of Disease

- Stable condition in 70% of patients

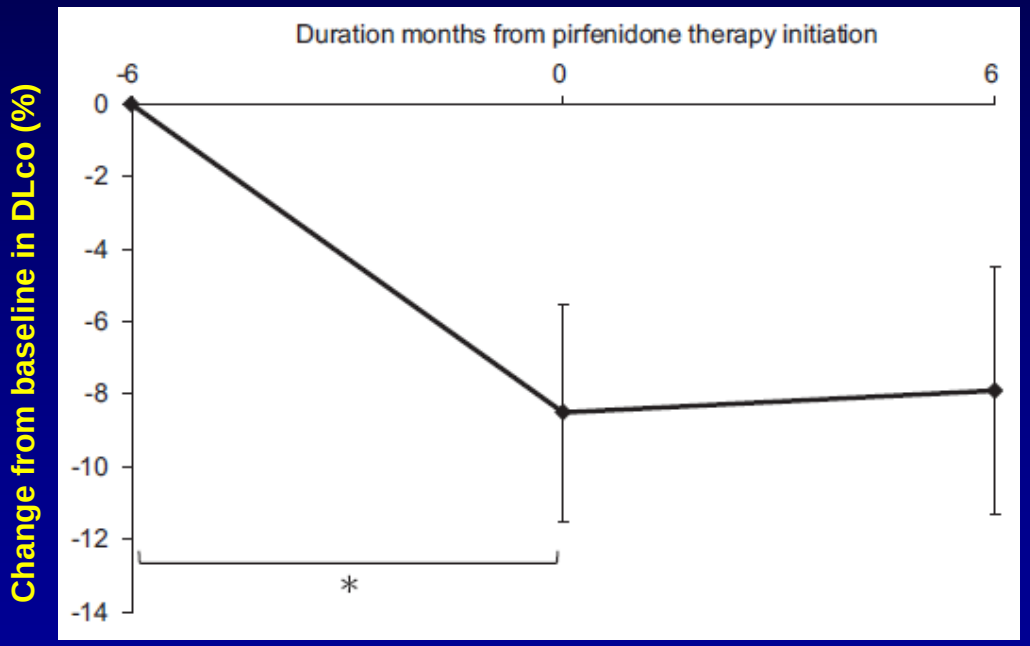
Bonella F et al. DMW 2013;138: 518-23

Change from 6 months before and with pirfenidone in FVC and DLco

N=36



N=24



Okuda et al, Respir Med 2013

Pirfenidone in real life: series reports

First Author	Year	Journal	Patients number	Efficacy
Bonella F	2013	Deutsche Medizinische Wochenschrift	45	Reduced decline in FVC in 70% of pts
Okuda R	2013	Respiratory Medicine	76	Reduced decline in FVC and DLco
Arai T	2013	Respiratory Investigation	41	Reduced decline in FVC and DLco
Wijsenbeek M	2013	Abstract ERS 2013	55	Reduced decline in FVC in 70-80% of pts
RavagliaC	2013	Abstract ERS 2013	81	Reduced decline in FVC in 59% of pt
Chauduri N	2013	Abstract ERS 2013	40	Reduced decline in FVC and DLco
Nieto Barbero NA	2013	Abstract ERS 2013	90	Reduced decline in FVC and DLco

Pirfenidone: Summary

- Pirfenidone is the first approved drug for treatment of mild to moderate IPF in Europe.
- Pirfenidone was tested in 5 randomized placebo-controlled trials including more than 1.600 IPF patients
- Pirfenidone has a clinically meaningful effect on FVC and exercise tolerance.
- Pirfenidone reduced disease progression and 1-year-mortality by 50%.
- The adverse events support a favourable risk-benefit ratio
  - increased GI und photosensitivity/skin reactions
  - only few leading to withdrawal

Thank you for your attention