Pirfenidone
NDA 22-535

Pulmonary-Allergy Drugs Advisory Committee

March 9, 2010

Introduction

Steven Porter, MD, PhD

Chief Medical Officer and Sr VP Clinical Affairs

InterMune

Proposed Indication

Pirfenidone is indicated for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function

Agenda

Introduction	**Steven Porter, MD, PhD** Chief Medical Officer & Sr VP Clinical Affairs *InterMune*
Unmet Medical Need	**Ron du Bois, MD** Professor of Medicine *National Jewish Health*
Efficacy	**Bill Bradford, MD, PhD** Sr VP, Clinical Science & Biometrics *InterMune*
Safety	**Steven Porter, MD, PhD**
Benefit / Risk	**Paul Noble, MD, FCCP** Professor of Medicine, Chief of Pulmonary, Allergy, & Critical Care Medicine *Duke University*

Invited External Experts

- **Gary Koch, PhD**
  University of North Carolina, Chapel Hill
- **Peter Kowey, MD**
  Jefferson Medical College
- **Willis Maddrey, MD**
  University of Texas, Southwestern
- **Brian Rogers, PhD, DABT**
  Pacific BioDevelopment, LLC
- **Chris Rubino, PharmD, BCPS**
  Ordway Research Institute
- **Derek Weycker**
  Policy Analysis Inc.
- **Jonathan Wilkin, MD**
  Wilkin Consulting, LLC

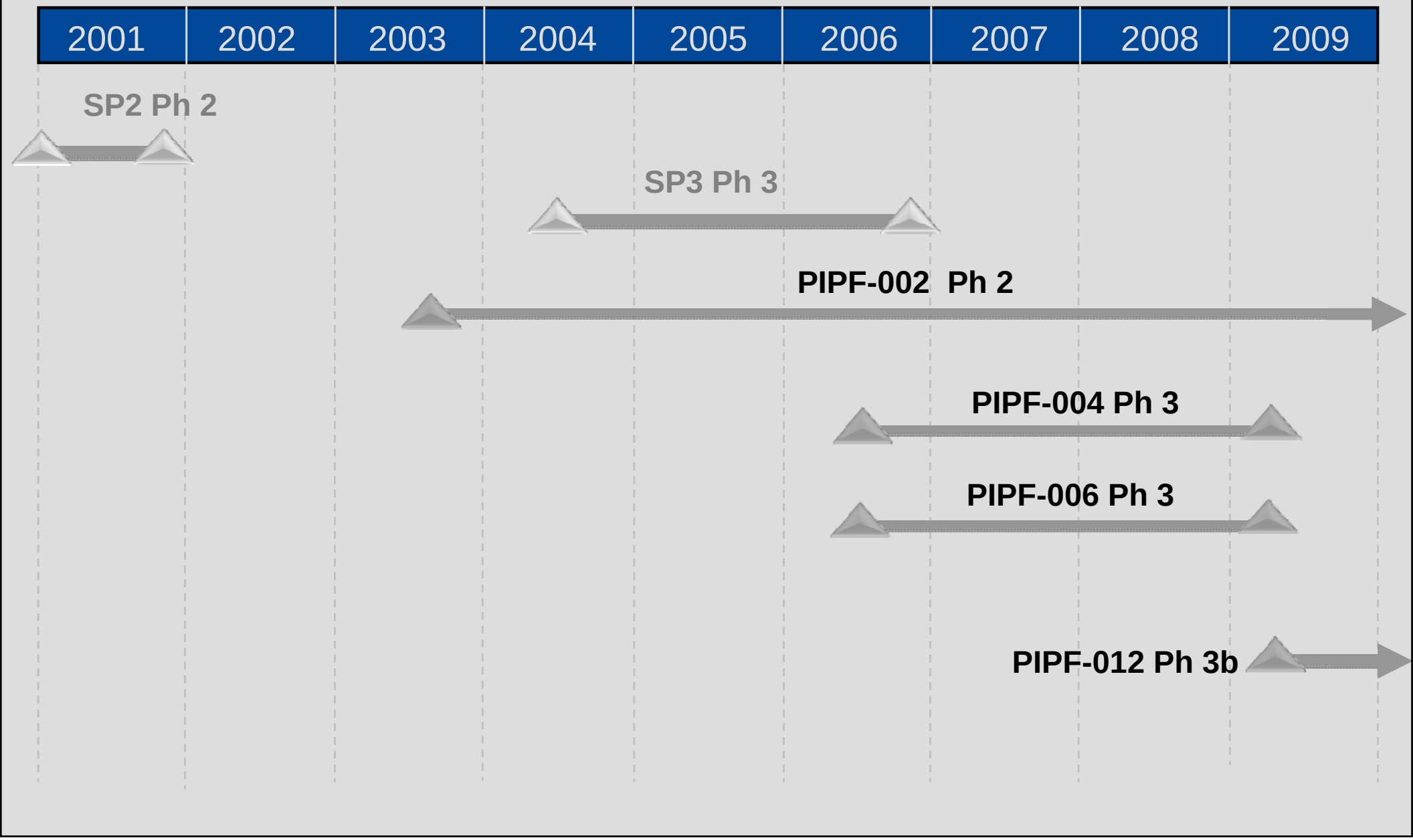
Unmet Medical Need in IPF

- IPF is a progressive, debilitating and fatal lung disease of unknown etiology
- No approved treatments in US; only drug approved worldwide is pirfenidone (Pirespa®) in Japan
- Current off-label treatments are unproven and have significant toxicities
- Unmet need for effective and safe treatments

Scientific Rationale for Development of Pirfenidone

- Orally available, synthetic, small molecule
- Exhibits anti-fibrotic and anti-inflammatory properties in *in vitro* studies and *in vivo* models
- Regulates TGF-β and TNF-α-mediated pathways
- Attenuates fibroblast proliferation and collagen deposition

Clinical Study Milestones



Summary
InterMune Phase 3 Studies

- PIPF-004 demonstrated benefit in primary endpoint of change in %FVC and secondary endpoint of progression-free survival
- PIPF-006 provided supportive evidence of treatment effect, but did not achieve primary endpoint
- Evidence of effectiveness supported by multiple consistencies within and between studies
- Favorable safety profile

Conclusion

- Extensive clinical development program for orphan indication
- Clinically meaningful treatment effect with pirfenidone
- Pirfenidone is the first therapy to demonstrate a favorable benefit-risk profile in treating patients with IPF

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Unmet Medical Need

Ron du Bois, MD

National Jewish Health

Unmet Medical Need

- The challenges in IPF
  - The extent of the problem
  - The nature of the disease
  - Management dilemmas
  - Clinical trial design

Idiopathic Pulmonary Fibrosis

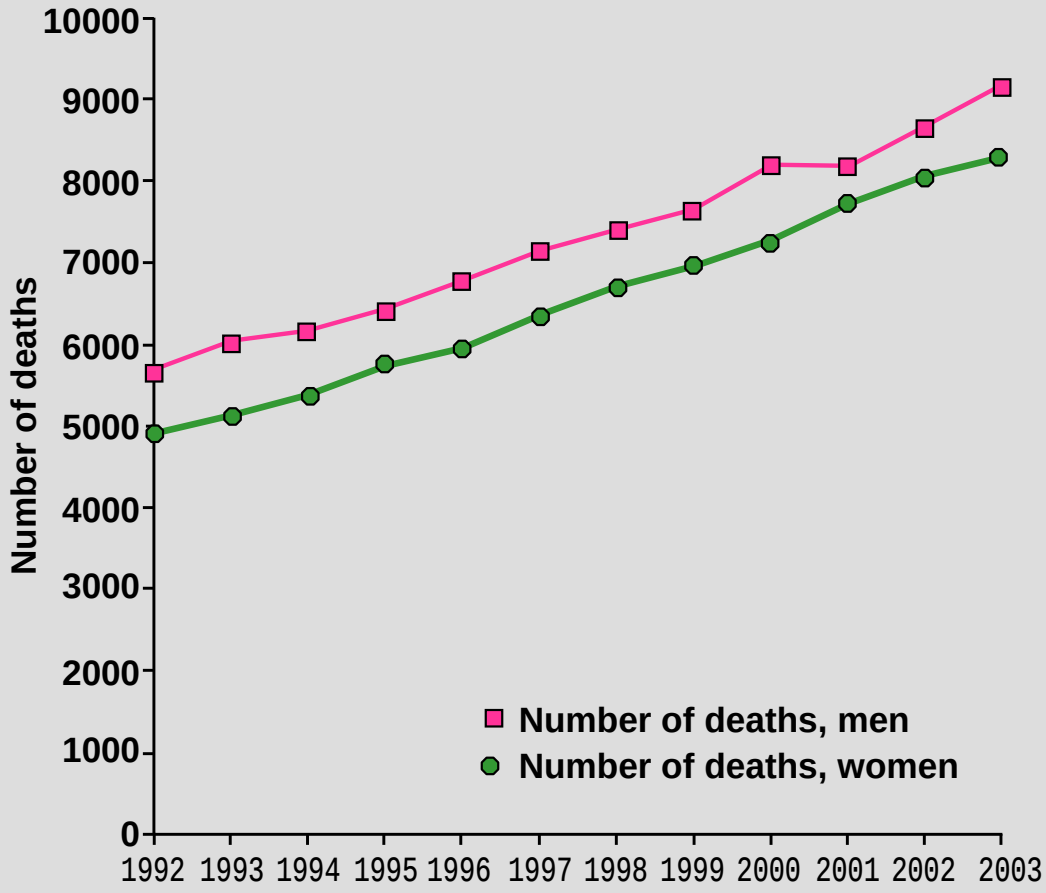
- Most patients are ≥ 50 yrs-old at diagnosis
- US incidence: ~30,000/yr[1]
  - Increasing incidence and IPF-related deaths[2,3]
- US prevalence: ~100,000[1]

1 Raghu G. *Am J Respir Crit Care Med.* 2006;174:810-816.
2 Raghu G. *Br J Cancer.* 2004;91:S3–S10.
3 Gribbin J. *Thorax*. 2006;61:980-985.

Pulmonary Fibrosis

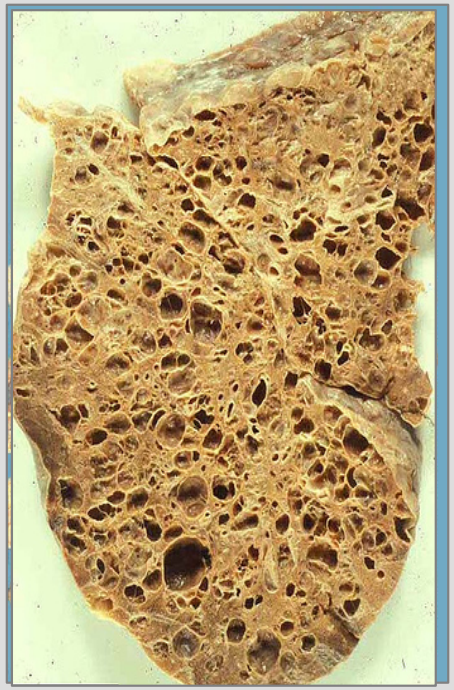
From 1992 to 2003[1]:

- **175,088 deaths due to pulmonary fibrosis**
- **Death rate worse than most lung diseases and many cancers**



1 Olson A. Am J Respir Crit Care Med. 2007;176:277-284.

Normal Lung to IPF Lung – The Process



Repeated injuries over many years; temporal and spatial heterogeneity in the pathology

Variable Clinical Course in IPF: Heterogeneity

- Disease progression heterogeneous within and between patients
- Insidious decline in pulmonary function
  - Patient incrementally becomes house-bound, oxygen-dependent, and then wheelchair-bound
- Ultimate outcome death

Challenges To IPF Clinical Management

- **Nature of IPF**
  - At diagnosis, IPF has usually been progressing for many years
  - At later stages, IPF pathology includes extensive and irreversible honeycomb lesions and fixed fibrosis
- **Impact of treatment**
  - Unlikely to improve lung function
  - Goal is to reduce decline by impacting most recent pathology–magnitude of change will be small
  - How can this impact be measured?

IPF Clinical Trial Design Challenges

- Few reported clinical trials of adequate size, scale, and duration
- Paucity of research to formally validate endpoints
  - ATS/ERS Guidelines indicated a range of indices that could be monitored in individual patients with IPF, but provided no guidelines for clinical trials
- No regulatory approval precedent
- Pirfenidone program in the vanguard of clinical trial process and conduct

Primary Clinical Endpoint: Reasons To Choose Change in % Forced Vital Capacity (FVC)

- Irreversible loss of lung function is hallmark of IPF
- FVC is widely used and accepted as clinically meaningful measure of IPF disease status (ATS/ERS 2000)
- Clinical meaningfulness of FVC illustrated by performance characteristics
  - Reliability: based on correlation between FVC at screening and baseline visits
  - Validity: FVC correlations with other measures of clinical status including dyspnoea and exercise capacity[1,2,3]
  - Responsiveness: relationship between categorical change in FVC, HRQL measures[4] and mortality

1 Swigris J et al . *CHEST. 2005*;127:284-294. 2 Papiris S et al. Resp Med. 2005;99:755-761. 3. Garin M et al. J Rheumatol. 2009;36:330-336. 4 Swigris et al Respir Med. 2010;104:296-304

FVC: Strong Predictor of Mortality in IPF

Risk of death at 1-yr: Cox proportional hazards model		HR	95% CI	p-value
%FVC change at 24 wks	≤ -10	2.89	1.70 - 4.92	< 0.001
	-5 to -9.9	1.82	1.16 - 2.87	0.009
	> -4.9 (referent)			
Baseline %FVC	≤ 50	2.42	0.98 - 5.95	0.055
	51 to 65	2.11	0.93 - 4.78	0.075
	66 to 79	1.33	0.56 - 3.15	0.521
	≥ 80 (referent)			

Analysis of all randomized patients (N = 1,156) in two phase 3 clinical trials in patients with IPF

du Bois R et al., 2009 ATS meeting.

Primary Clinical Endpoint: Analysis of Change in % Forced Vital Capacity (FVC)

- Primary analysis tests differences between groups
- Must examine individual patient changes to understand meaning of treatment group differences
  - Categorical FVC Change
  - PFS
- Magnitude of individual patient benefit not always reflected by group mean differences

Medical Need Summary

- IPF is a progressive, irreversible, ultimately fatal lung disease characterized by variable decline in lung function
- No approved treatments in US
  - no pipeline drug near regulatory approval
- Heterogeneous disease; categorical changes in FVC most clinically meaningful - valid and responsive
- Urgent need for treatments that are safe and offer evidence of effectiveness for IPF
  - Pirfenidone program takes account of the nature of disease, the magnitude of possible change in lung function, and most appropriate primary endpoint

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Efficacy of Pirfenidone

Bill Bradford, MD, PhD

Sr VP, Clinical Science and Biometrics

Pirfenidone Benefits Patients with IPF

- PIPF-004: Robust and persuasive results on primary endpoint and two clinically important secondary endpoints
- PIPF-006: Supports PIPF-004 with noteworthy consistencies; primary endpoint not achieved
- Pooled results provide precise estimates of clinically meaningful effects on %FVC, PFS, and 6MWT
- Collective evidence demonstrates clinical benefit of pirfenidone

Overview of Presentation

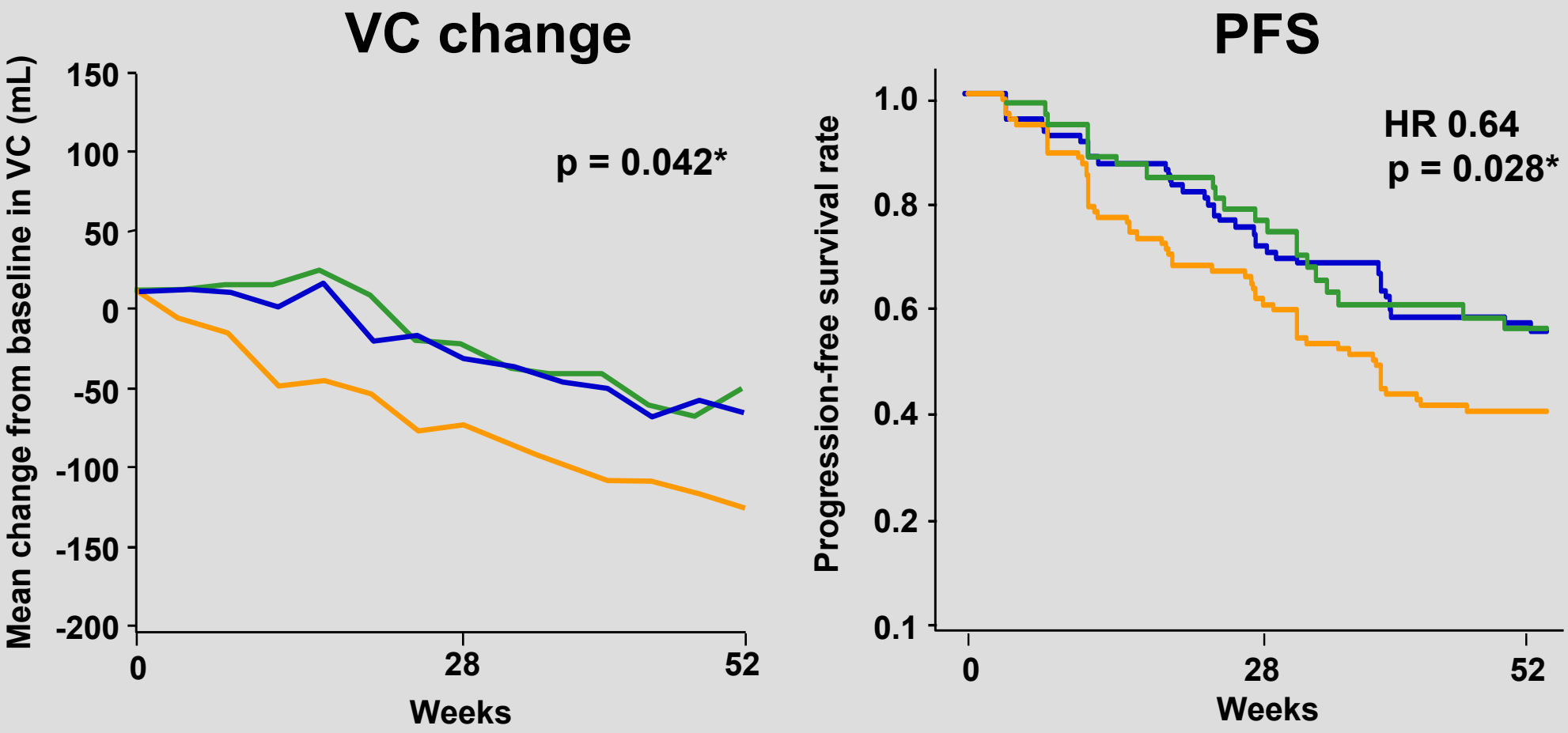
- Shionogi studies
- InterMune Phase 3 studies
  - PIPF-004
  - PIPF-006
  - Comparison of PIPF-004 and PIPF-006
- Pooled analyses of PIPF-004 and PIPF-006

Shionogi Studies

Shionogi IPF Studies

- SP2 (Phase 2)
  - 52-wks, but terminated early for efficacy (N = 109)
  - VC endpoints favor pirfenidone
- SP3 (Phase 3)
  - 52-wk treatment (N = 267)
  - 2:2:1 randomization
    - Pirfenidone 1800 mg/d
    - Placebo
    - Pirfenidone 1200 mg/d
  - Eligibility
    - IPF diagnosis confirmed by central review panel
    - Mild-to-moderate impairment in lung function
  - Primary endpoint: Change in VC at Wk 52

SP3 Efficacy Outcomes



*Pirfenidone 1800 mg/d vs placebo.

Shionogi Studies Informed Design of InterMune Phase 3 Studies

- Study population: Mild-to-moderate impairment in lung function
  - Most likely to benefit from intervention that slows irreversible loss of lung function
- Primary endpoint: Change in lung function
- Dose selection: Similar weight-normalized dose

InterMune Phase 3 Studies

PIPF-004

PIPF-006

Study Design
PIPF-004

- Multinational RDBPC trial
- 2:2:1 randomization
  - Pirfenidone 2403 mg/d
  - Placebo
  - Pirfenidone 1197 mg/d
- Study treatment and assessments until 72 wks after last patient enrolled
- Eligibility
  - Confident clinical, HRCT diagnosis
  - %FVC ≥ 50% and %DL_{CO} ≥ 35%
  - %FVC < 90% or %DL_{CO} < 90%
  - Exclusions: Obstructive lung disease, patients on medications for IPF

Primary Efficacy Endpoint
PIPF-004

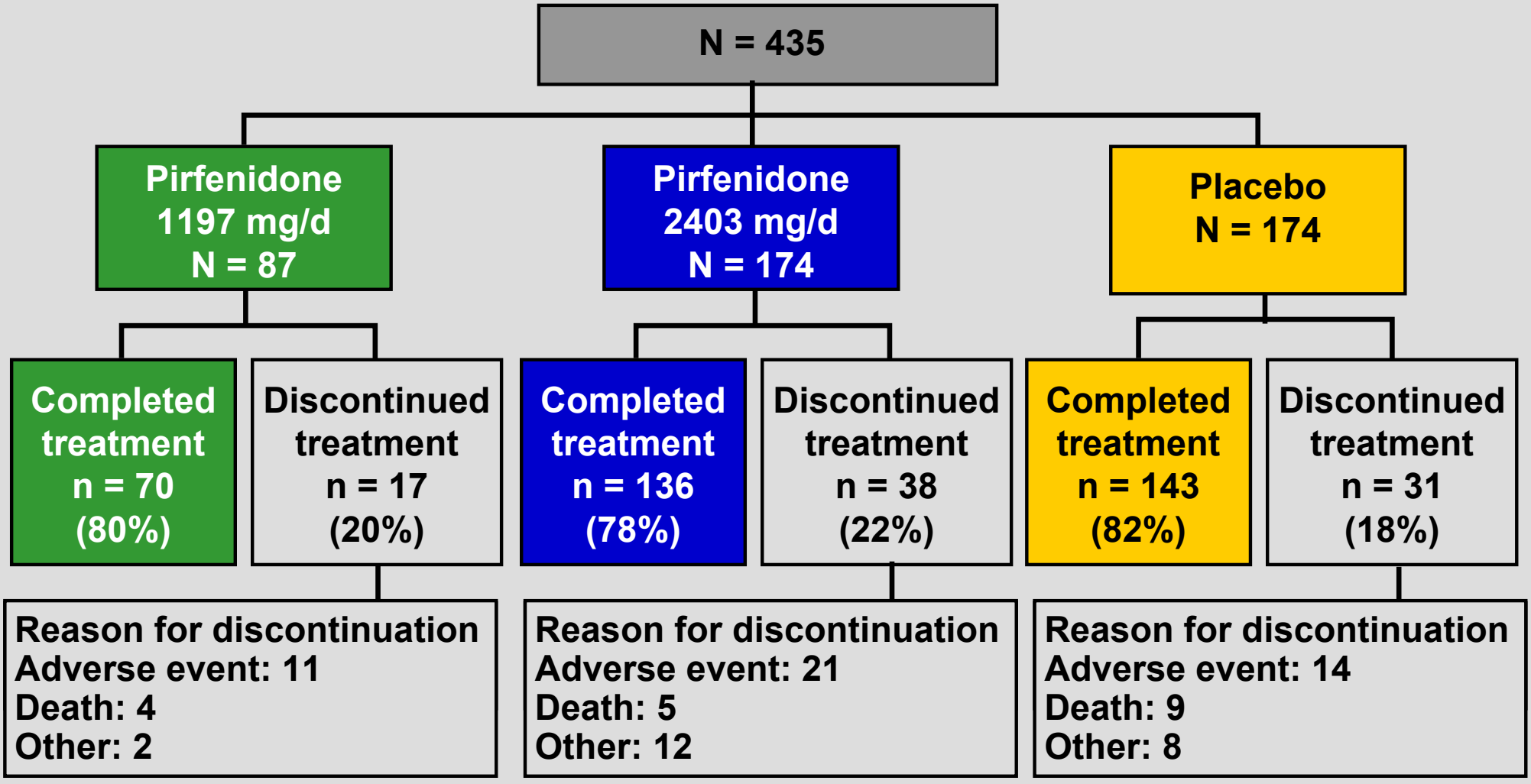
- Percent predicted FVC (%FVC) change at Wk 72
  - FVC assessed every 12 wks under rigorous protocol based on ATS guidelines
- Analysis: rank ANCOVA in ITT population
  - Deaths assigned worst ranks; other missing data imputed based on similar patients
- Magnitude of treatment effect
  - Population: difference in group means
  - Patient: categorical change in %FVC

Secondary and Exploratory Endpoints
PIPF-004

- Secondary endpoints
  - Categorical %FVC
  - PFS
  - 6-Minute Walk Test (6MWT) Distance
  - Lowest SpO_2 during 6MWT
  - $\%DL_{CO}$
  - Dyspnea (UCSD SOBQ)
  - Time to worsening
- Prespecified exploratory endpoints
  - Survival

UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

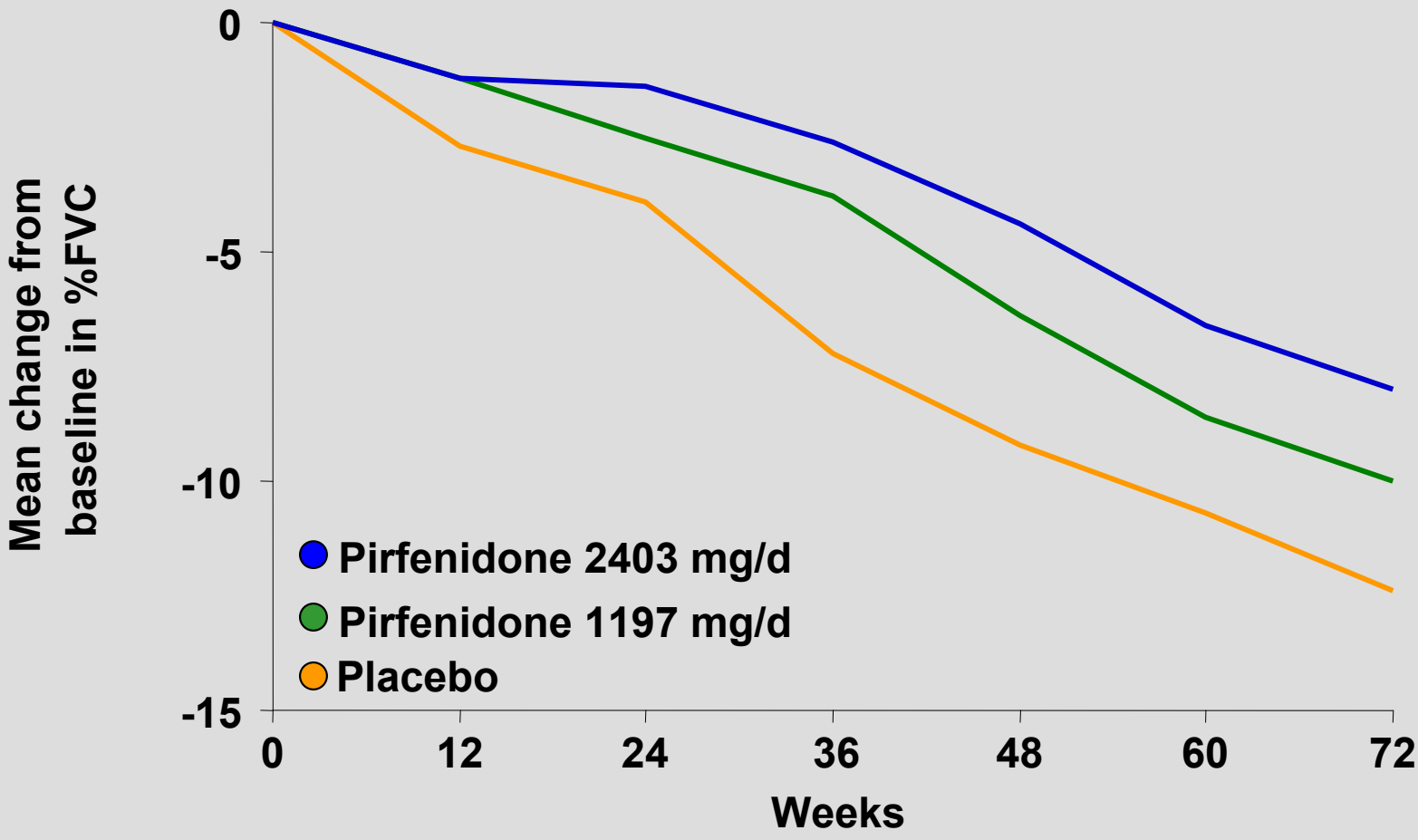
Patient Disposition
PIPF-004



Demographic and Baseline Characteristics
PIPF-004

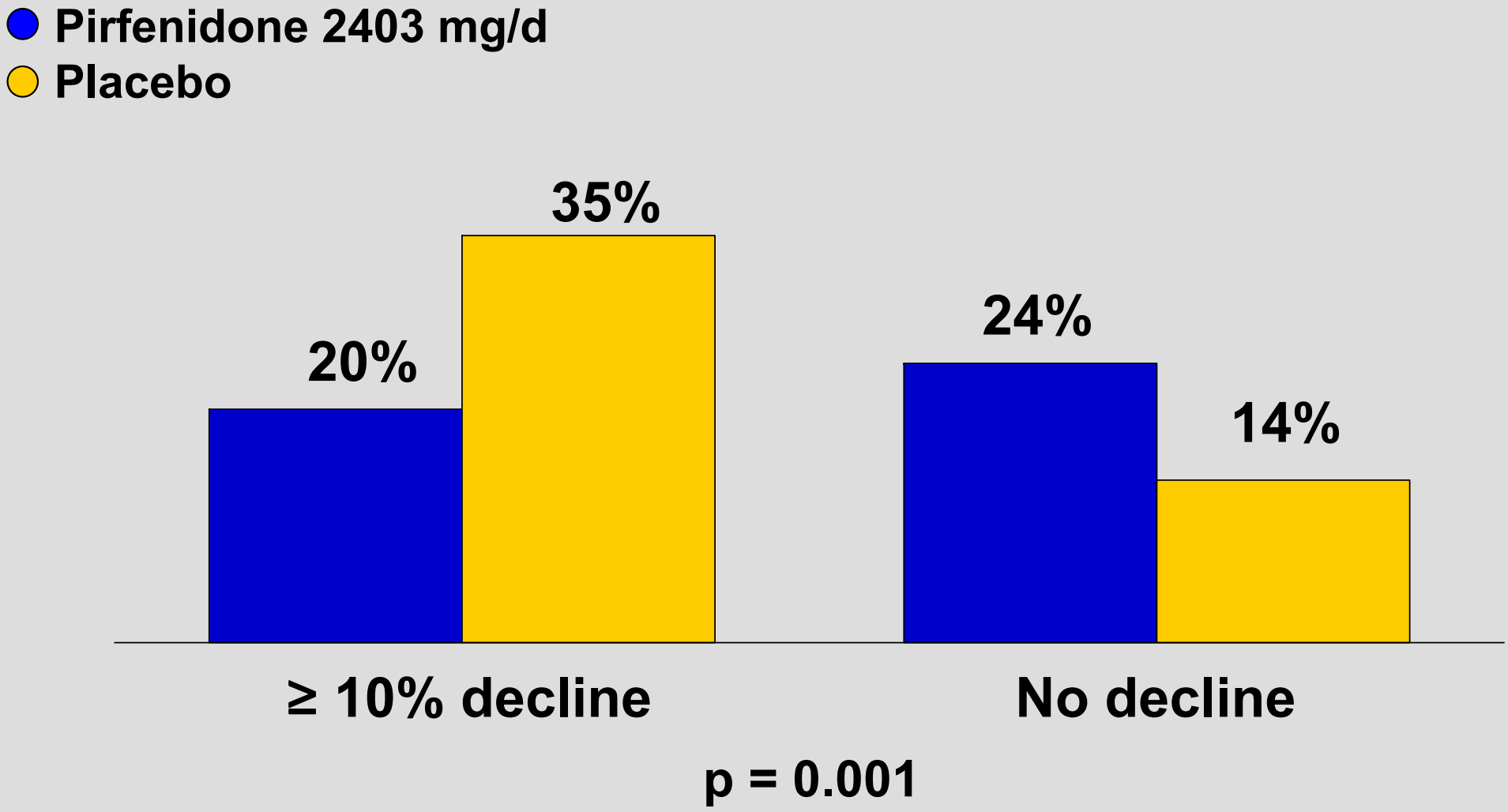
Characteristic	Pirfenidone 1197 mg/d N = 87	Pirfenidone 2403 mg N = 174	Placebo N = 174
Mean age, yrs	68	66	66
Ex-US enrollment, %	33	35	35
%FVC, %	76.4	74.5	76.2
$\%DL_{CO}$, %	47.2	46.4	46.1
Supplemental O_2 use, %	17.4	16.7	14.4
HRCT “Definite IPF”, %	95.4	91.4	94.3

Primary Endpoint: %FVC Change at Wk 72
PIPF-004

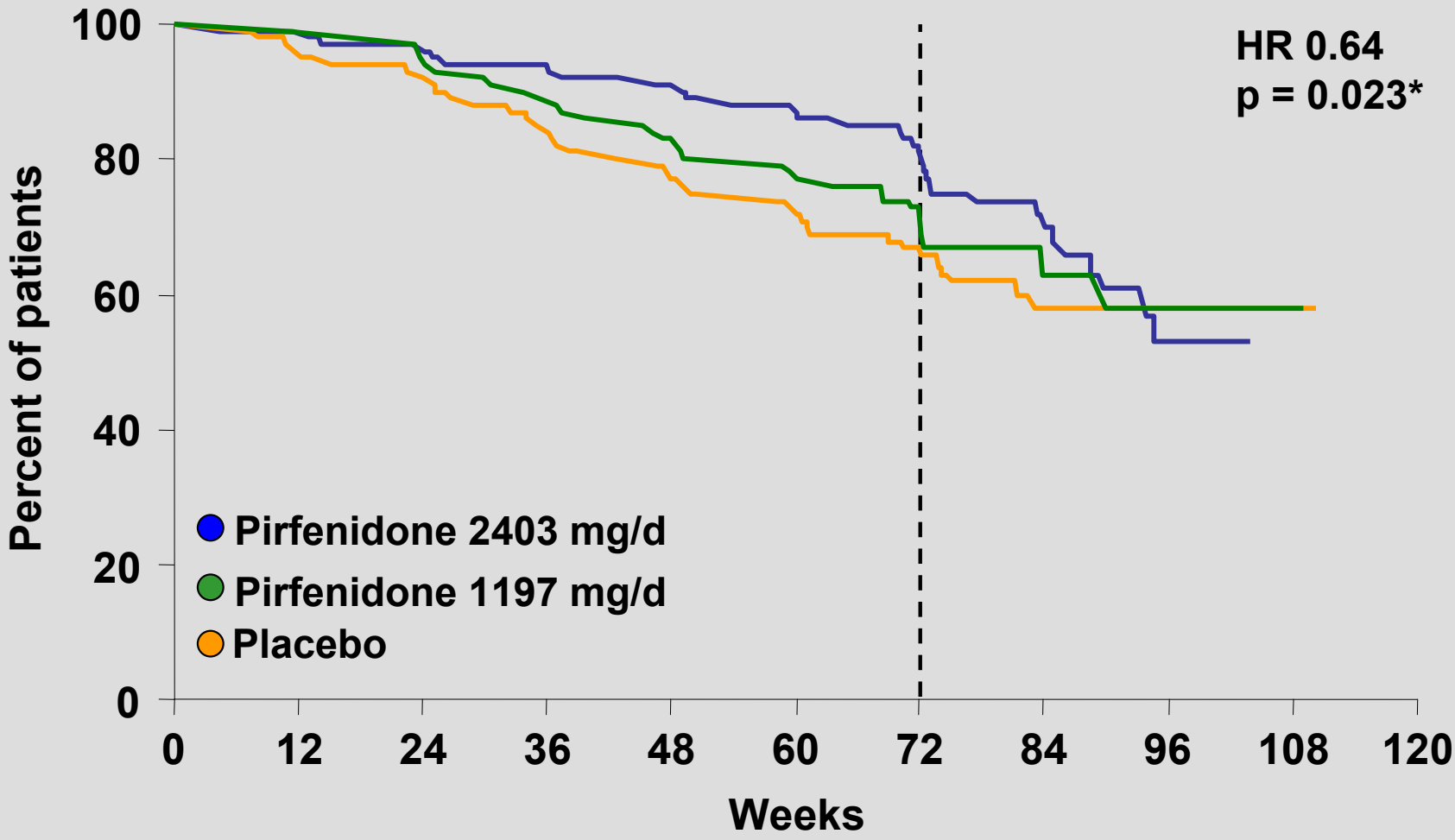


Pirfenidone 2403 mg/d vs Placebo						
Absolute difference, %	1.4	2.5	4.6	4.8	4.1	4.4
Relative difference, %	53.5	65.2	63.7	52.3	38.3	35.3
p-value	0.061	0.014	< 0.001	< 0.001	< 0.001	0.001

Categorical %FVC Change at Wk 72
PIPF-004

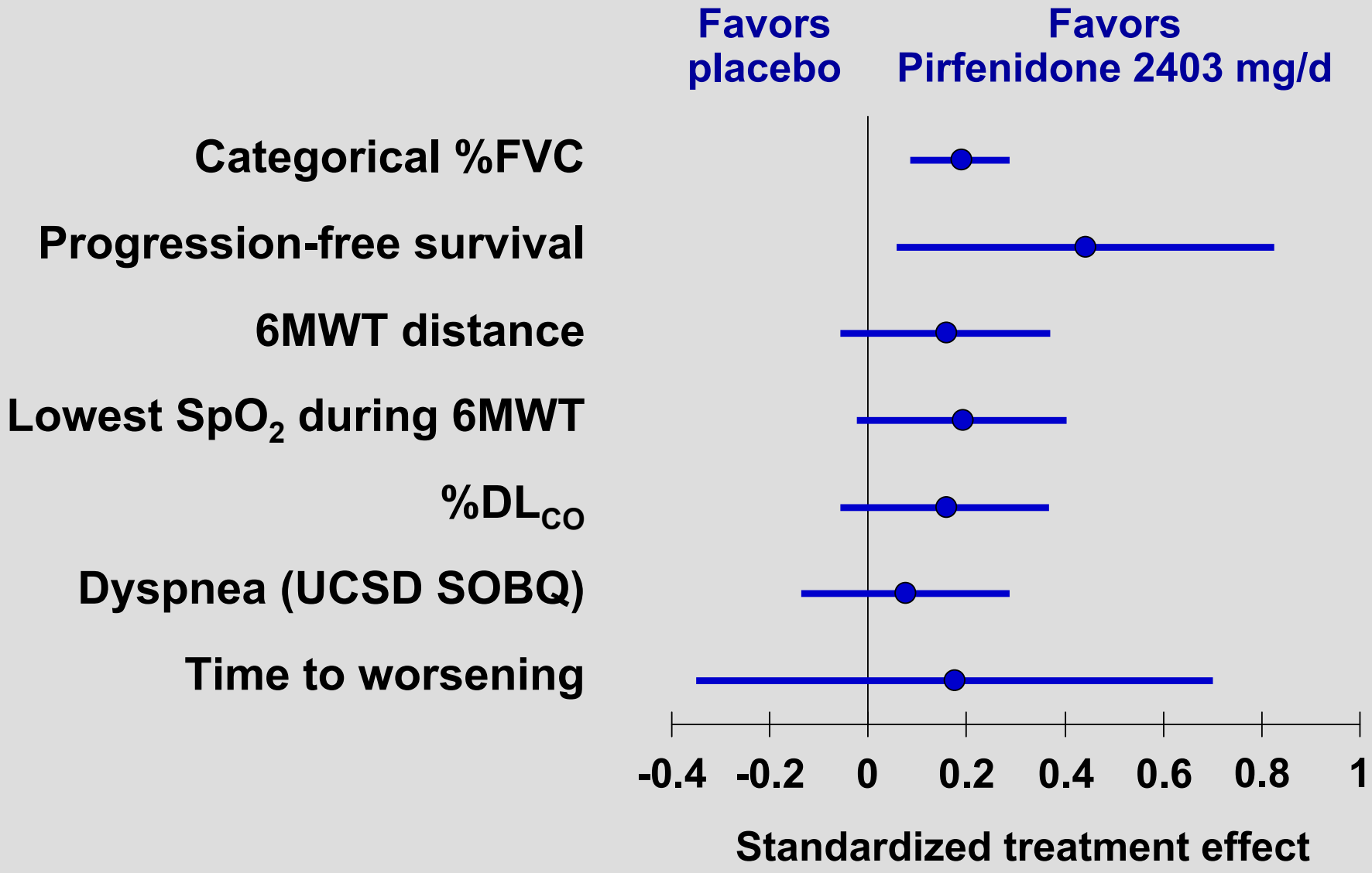


Progression-Free Survival
PIPF-004



* Pirfenidone 2403 mg/d vs placebo.

All Secondary Endpoints
PIPF-004



Efficacy Summary
PIPF-004

- Excellent study conduct
- Clinical benefit on primary endpoint (%FVC change)
- Clinically meaningful treatment effect on two secondary endpoints
  - Categorical %FVC change
  - Progression-free survival
- Dose-response relationship supports efficacy findings and selection of 2403 mg/d dose

InterMune Phase 3 Studies

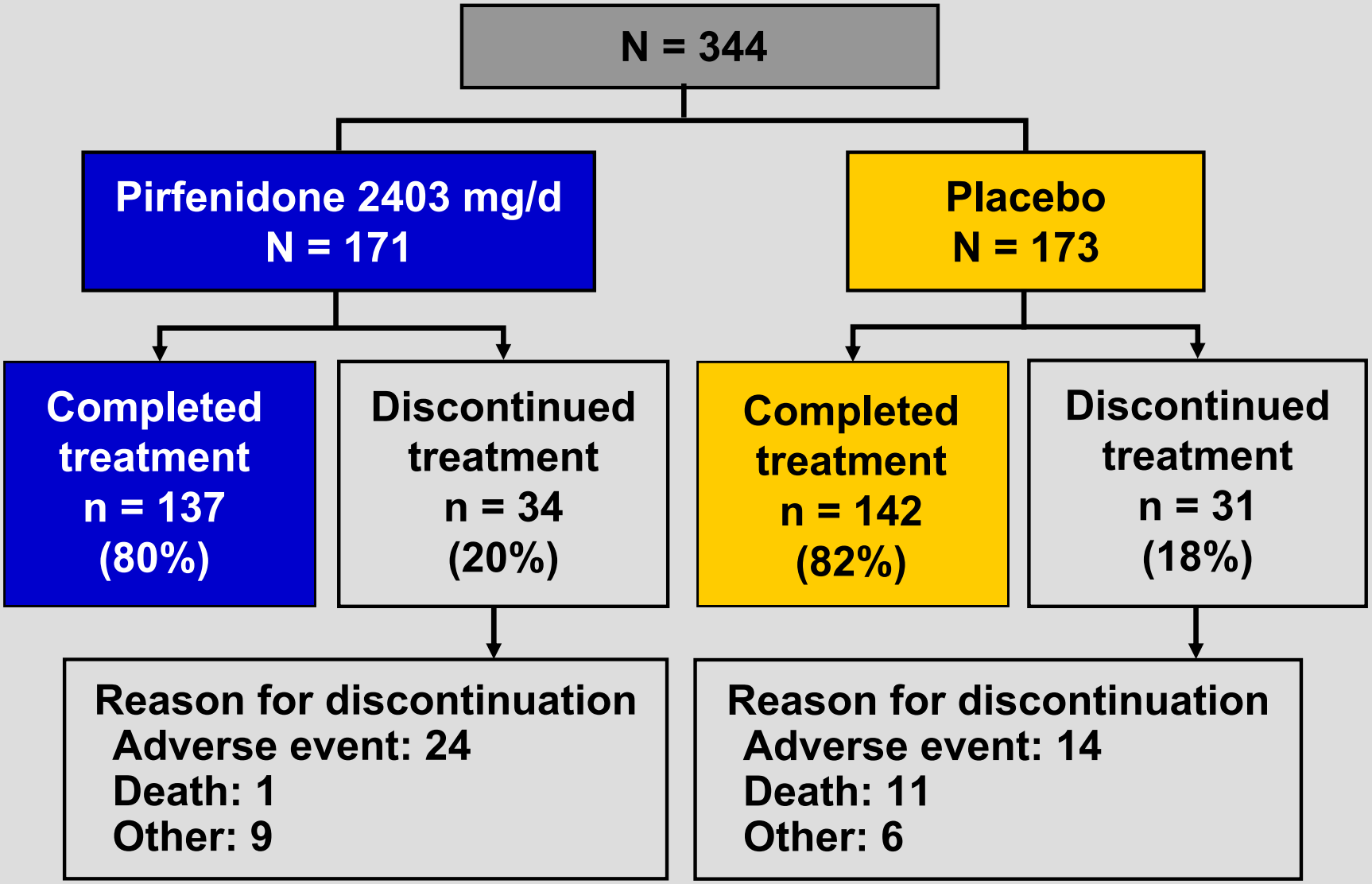
PIPF-004

PIPF-006

Study Design
PIPF-006

- Multinational RDBPC trial with 1:1 randomization
  - Pirfenidone 2403 mg/d
  - Placebo
- Study design, conduct otherwise identical to 004
  - Exception: HRCT change in fibrosis at Wk 72

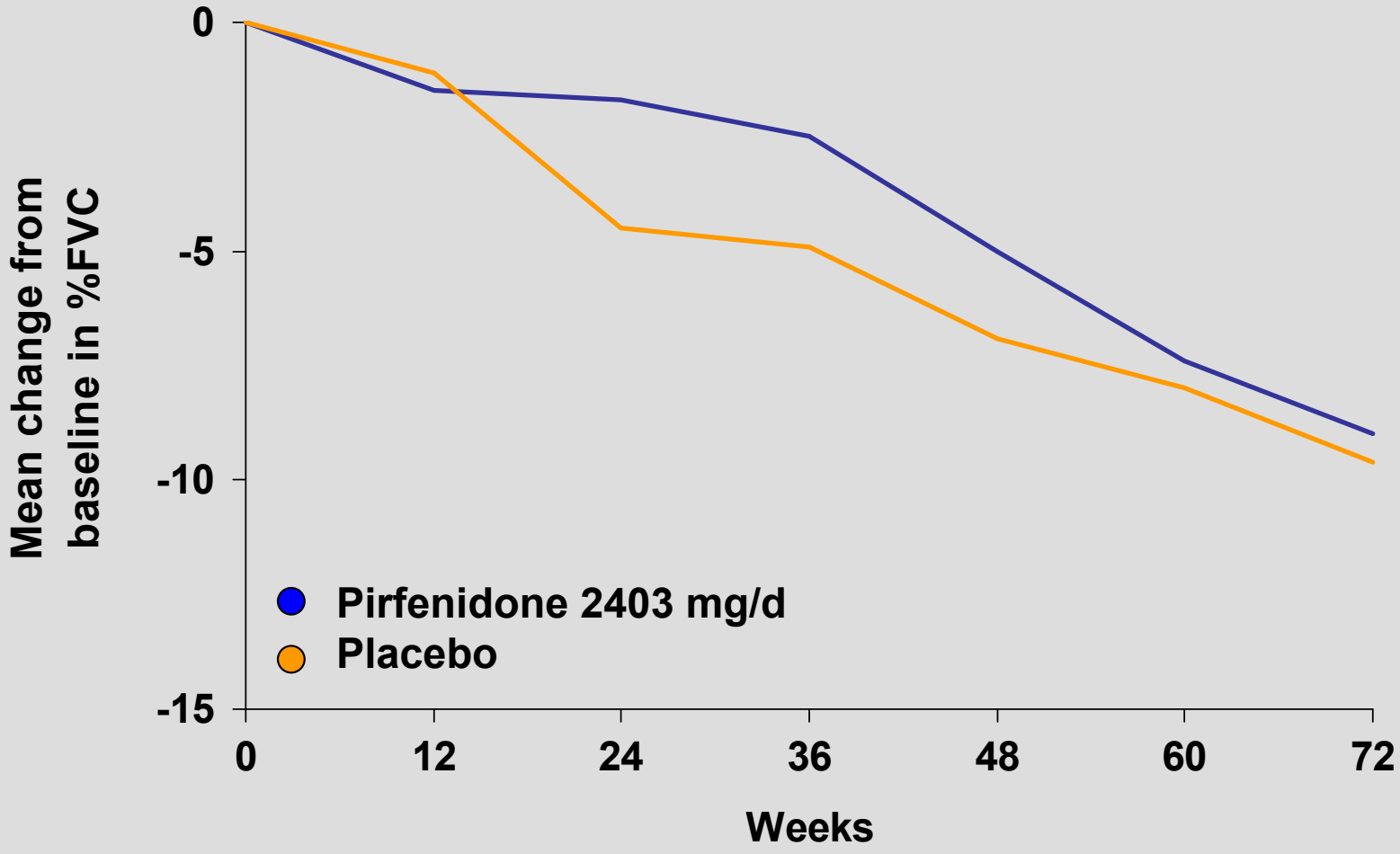
Patient Disposition
PIPF-006



Demographic and Baseline Characteristics
PIPF-006

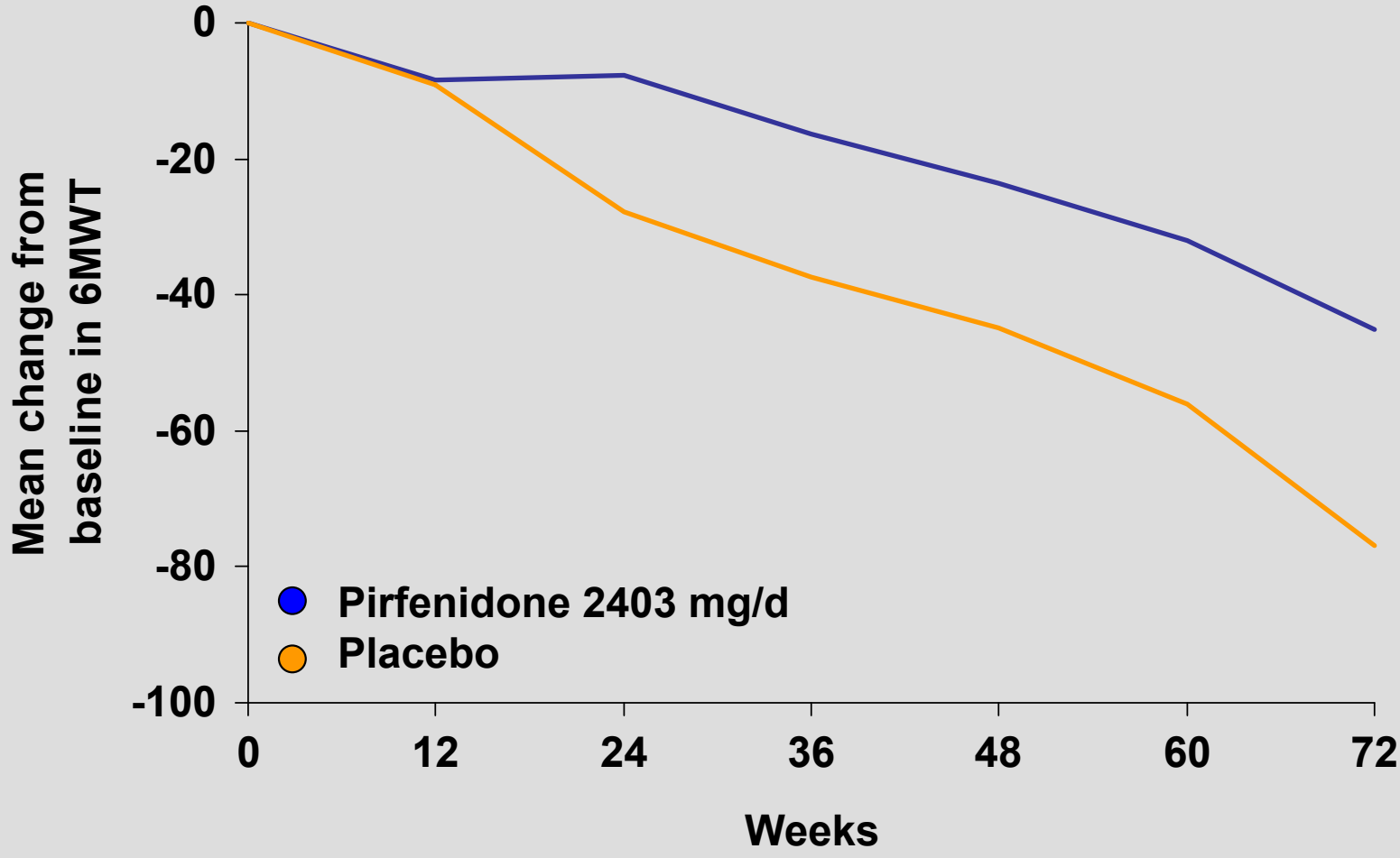
Characteristic	Pirfenidone 2403 mg N = 171	Placebo N = 173
Mean age, yr	67	67
Ex-US enrollment, %	14	13
%FVC, %	74.9	73.1
$\%DL_{CO}$, %	47.8	47.4
Supplemental O_2 use, %	28.1	28.3
HRCT “Definite IPF”, %	87.6	91.3

Primary Endpoint: %FVC Change at Wk 72
PIPF-006



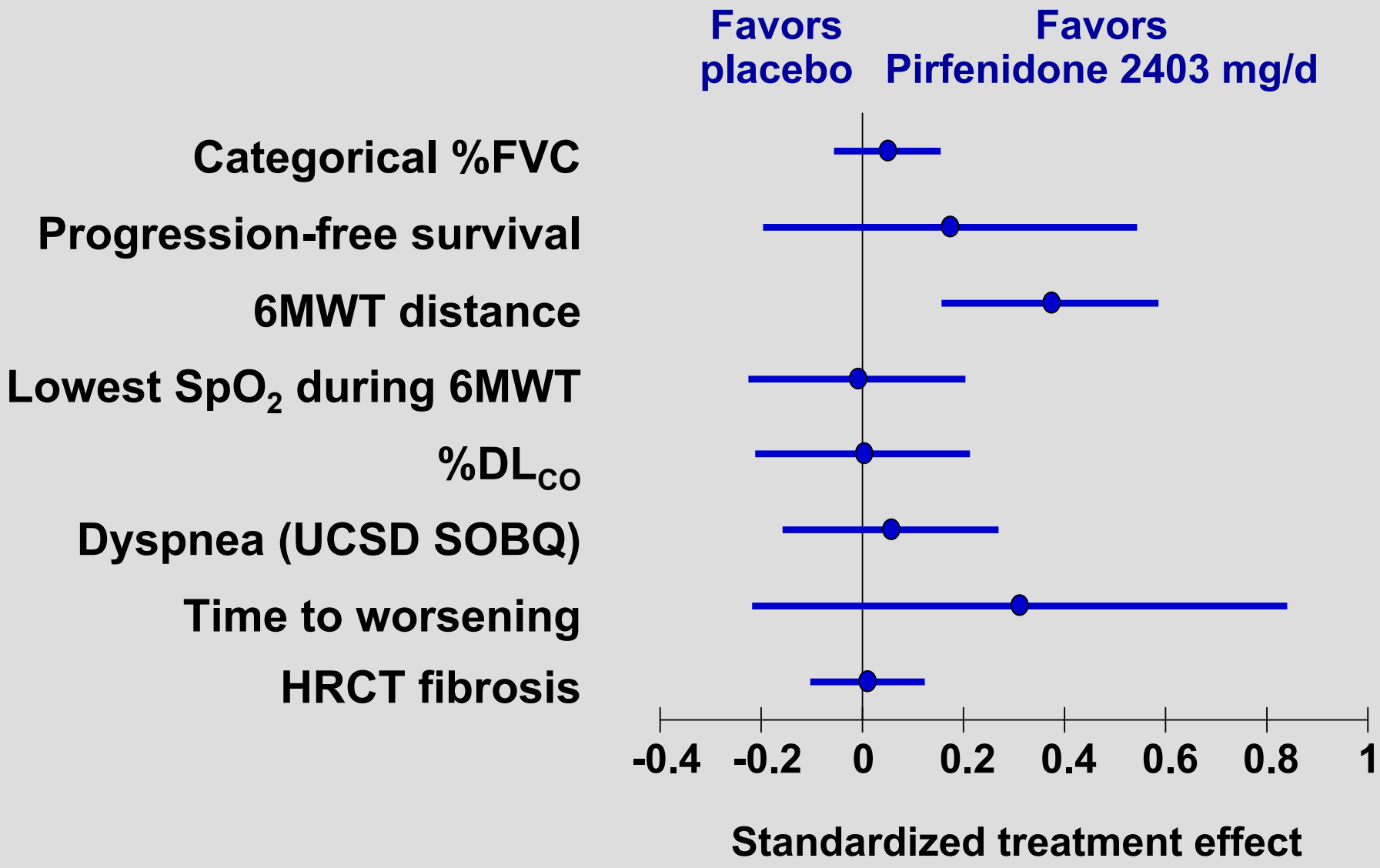
Absolute difference, %	-0.4	2.8	2.4	1.9	0.6	0.6
Relative difference, %	-31.5	62.1	48.2	27.3	7.6	6.5
p-value	0.021	< 0.001	0.011	0.005	0.172	0.501

6MWT Distance Change at Wk 72
PIPF-006



Absolute difference, m	1	20	21	21	24	32
Relative difference, %	8.1	72.3	56.2	47.8	43.1	41.3
p-value	0.975	0.038	0.044	0.023	0.014	< 0.001

All Secondary Endpoints
PIPF-006

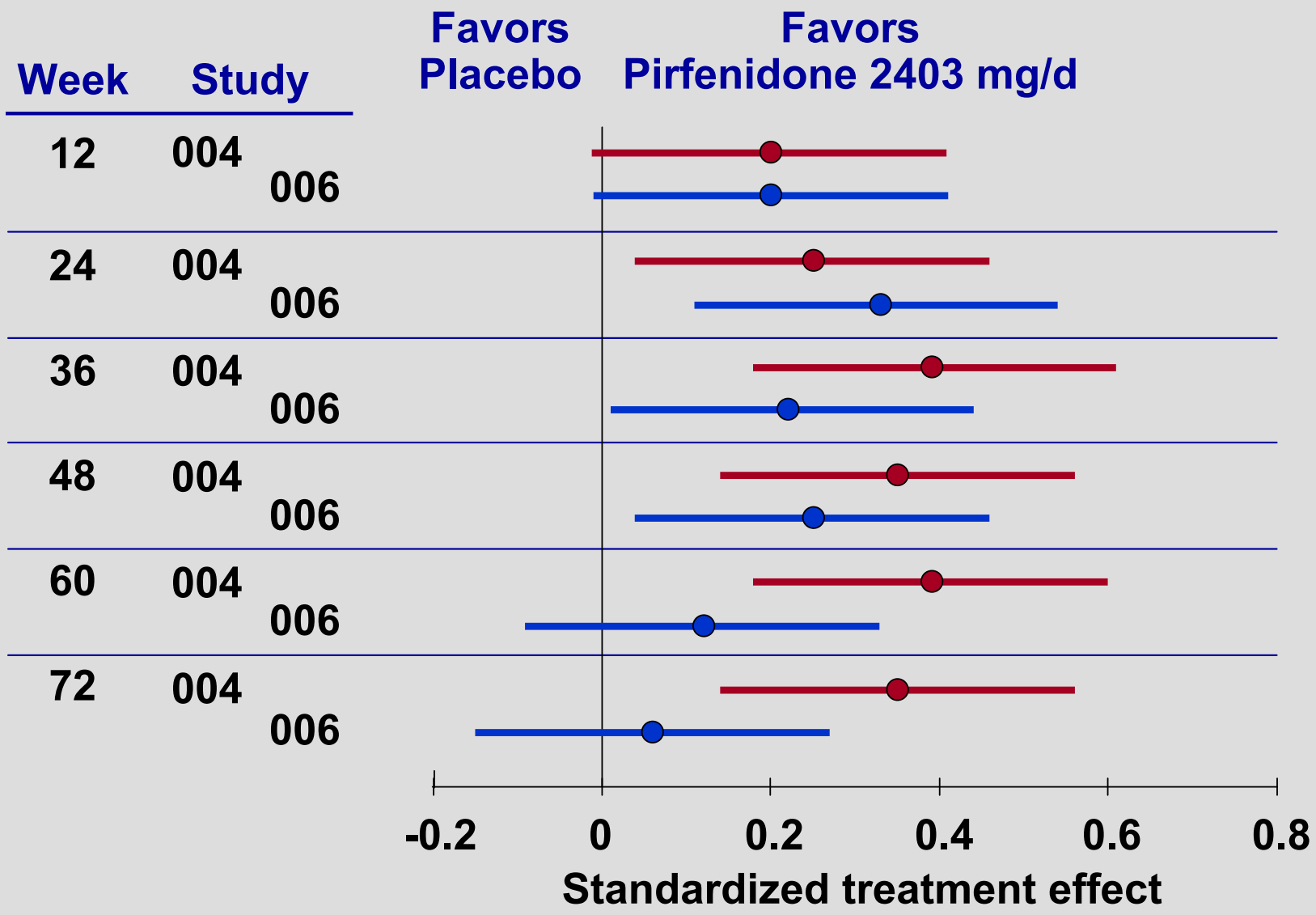


Efficacy Summary
PIPF-006

- Excellent study conduct
- Primary endpoint at Wk 72 not achieved
  - Treatment effect on %FVC observed at time points through Wk 48
- Clinically meaningful treatment effect observed on 6MWT distance

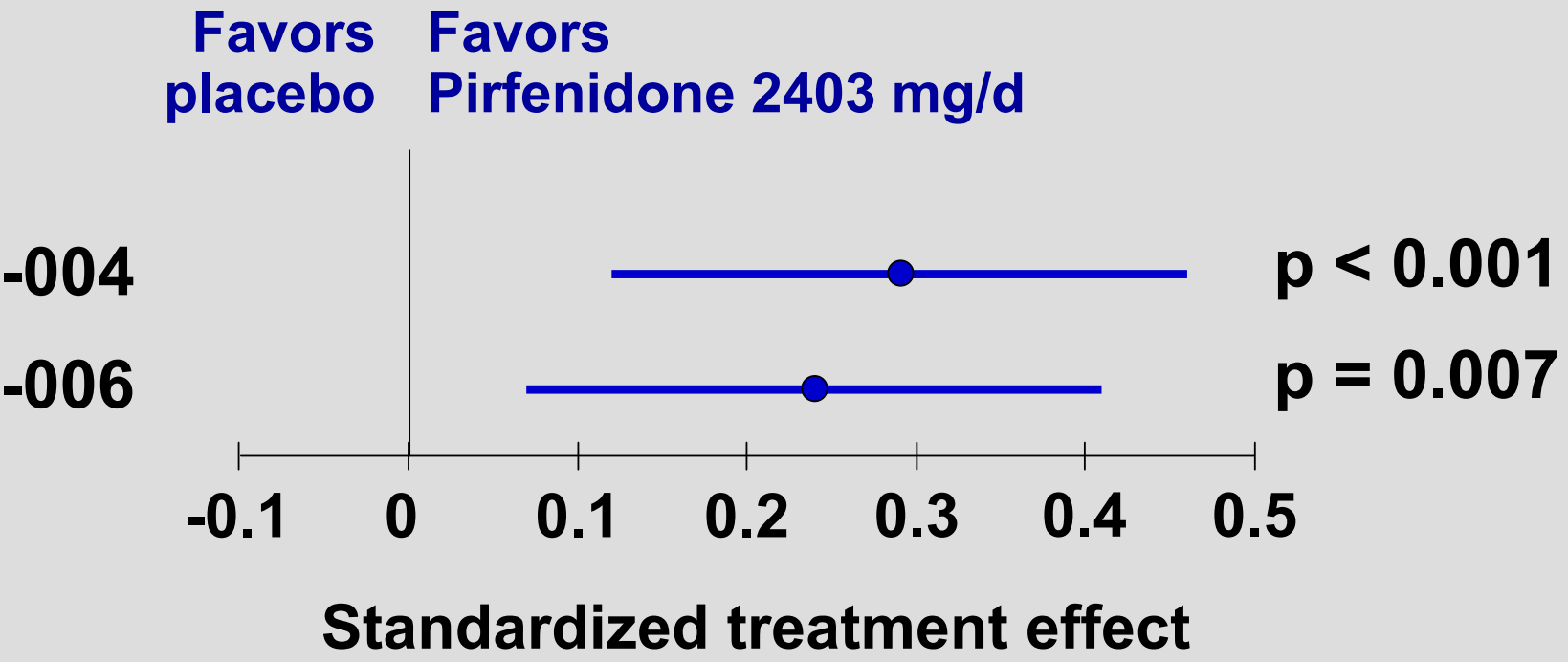
Comparison of PIPF-004 and PIPF-006

Landmark Analyses of %FVC

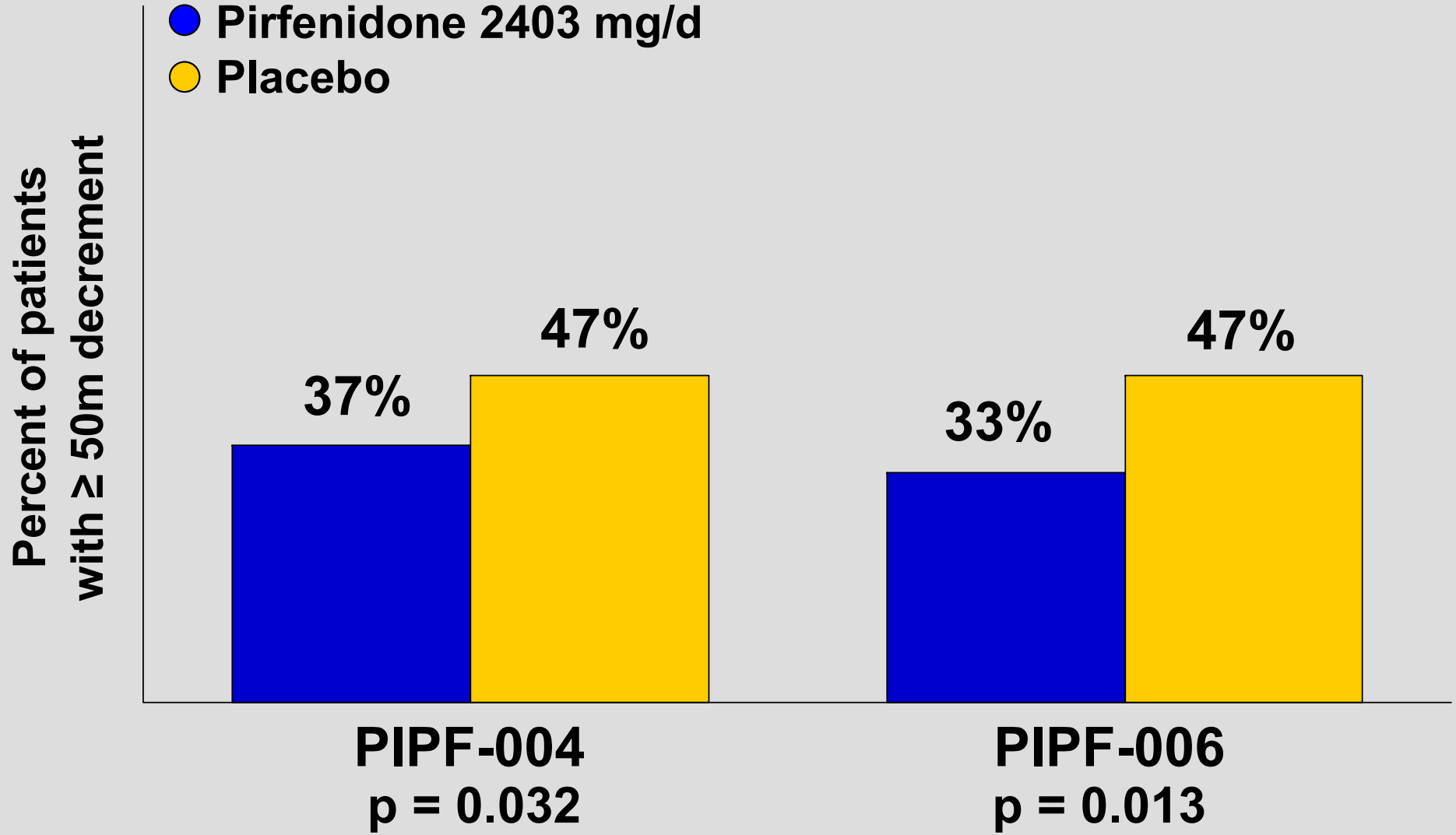


Repeated Measure Analysis of %FVC

- Evaluates average treatment effect over complete study
- Analysis based on ranked %FVC change



Post Hoc Analysis: 6MWT Distance Decrement ≥ 50 Meters at Wk 72



Exploratory Analyses: Differences in Wk 72 FVC Outcomes

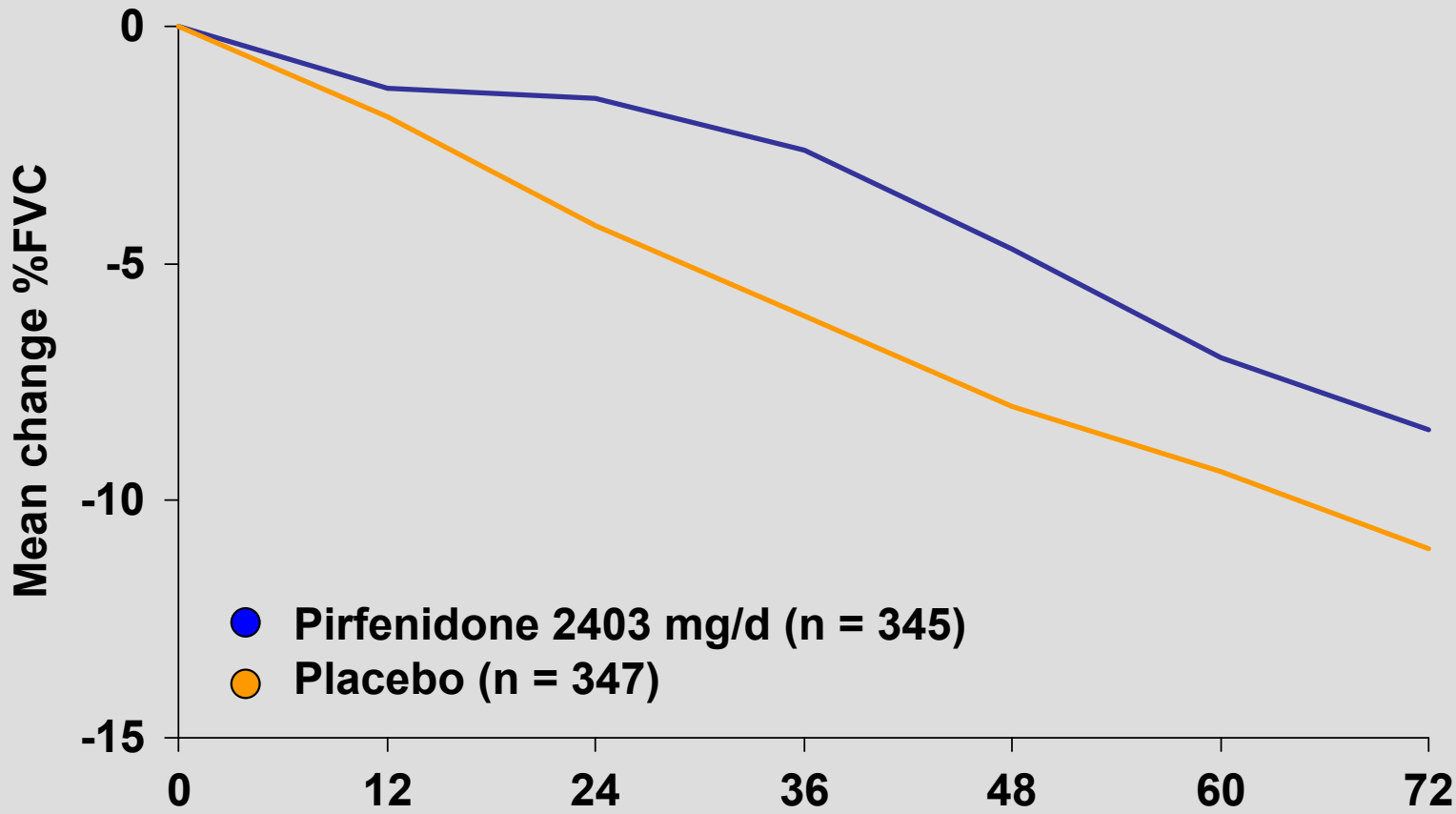
- Extensive analyses conducted
  - Demographic and baseline characteristics
  - Patient disposition
  - Concomitant medications
  - Numerous other variables
- Differences not clearly explained by imbalances across studies
- Observed differences likely related to variability in rates of FVC decline

Pooled Analyses of PIPF-004 and PIPF-006

Rationale for Prespecified Pooled Analyses to Support Efficacy

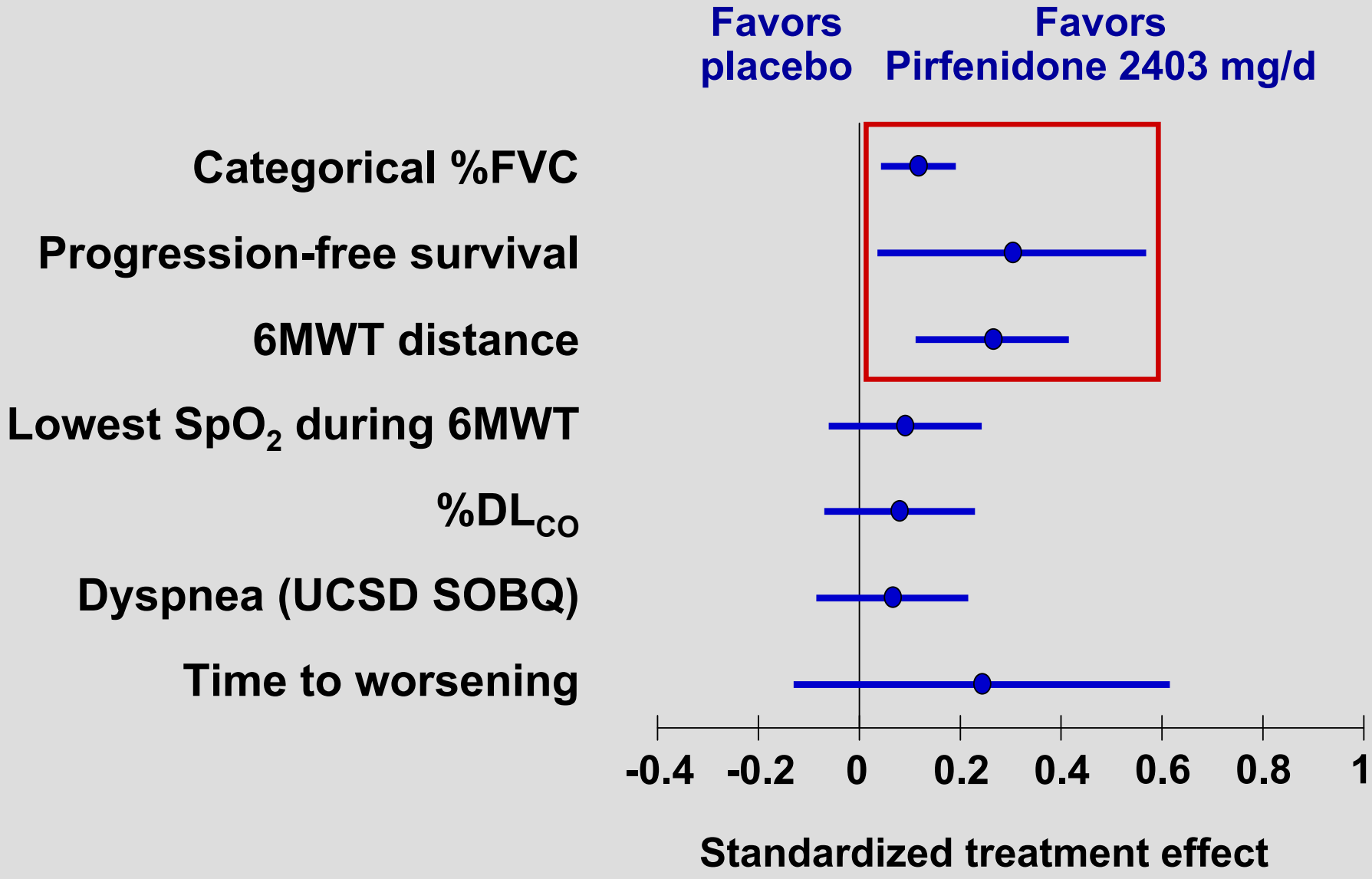
- Limited preliminary data to guide powering of endpoints
- PIPF-004 and PIPF-006 designed as nearly identical studies to facilitate pooling
- Individual study results support pooling
  - Overall results directionally similar
  - No treatment by study interaction
- Pooled results provide most precise estimates of effect

Primary Endpoint: %FVC Change at Wk 72
Pooled PIPF-004 and PIPF-006

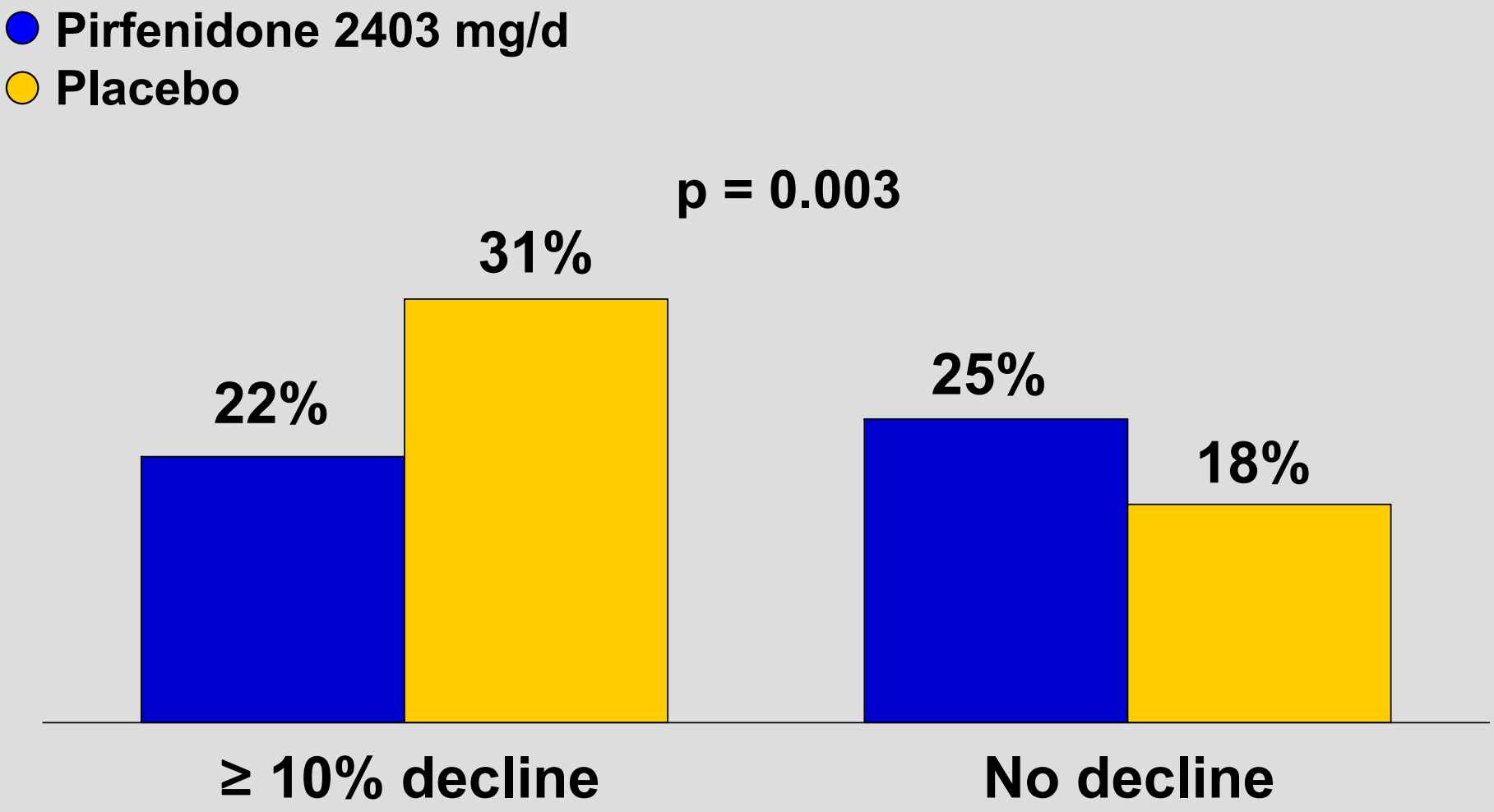


Mean change						
Absolute difference	0.5%	2.7%	3.5%	3.3%	2.4%	2.5%
Relative difference	28.5%	63.6%	57.5%	41.6%	25.1%	22.8%
p-value	0.003	< 0.001	< 0.001	< 0.001	< 0.001	0.005

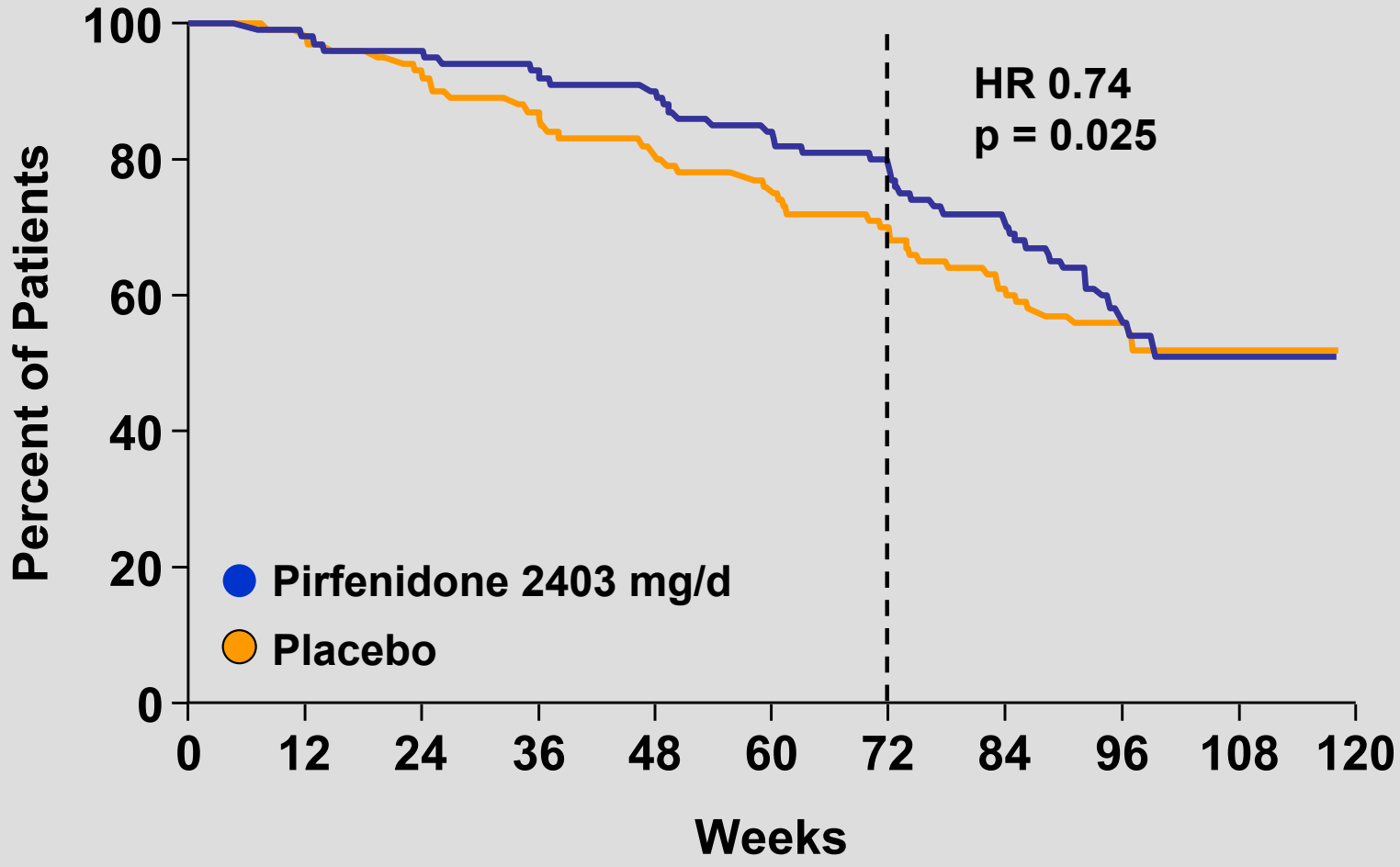
Secondary Endpoints
Pooled PIPF-004 and PIPF-006



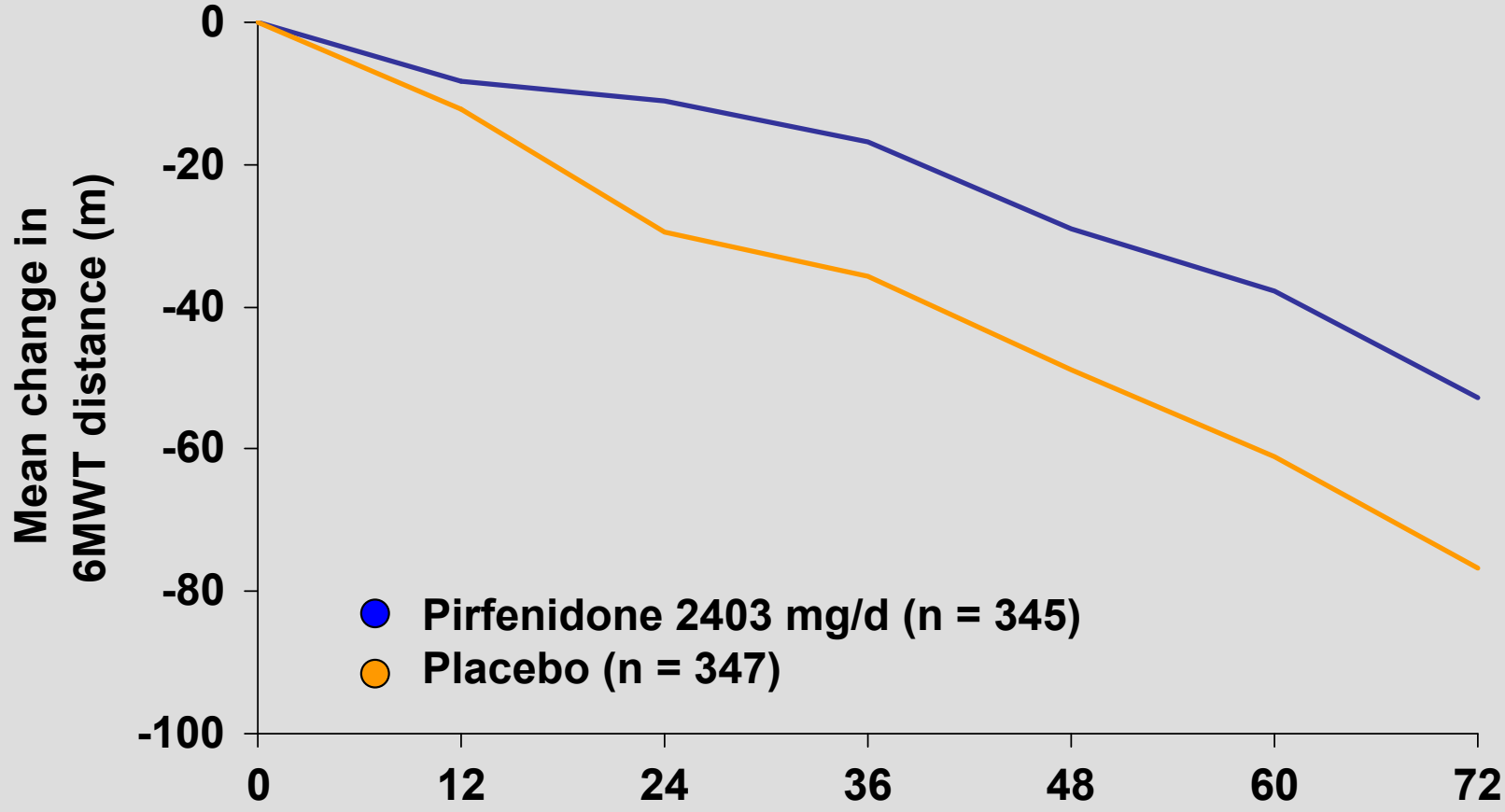
Categorical %FVC Change at Wk 72
Pooled PIPF-004 and PIPF-006



Progression Free Survival
Pooled PIPF-004 and PIPF-006



6MWT Distance Change at Wk 72
Pooled PIPF-004 and PIPF-006



Absolute difference, m	3.9	18.6	18.7	19.8	23.3	24.0
Relative difference, %	32.2	62.8	52.5	40.6	38.2	31.2
p-value	0.760	0.042	0.053	0.004	0.002	< 0.001

Survival Time Analyses
Pooled PIPF-004 and PIPF-006

	Deaths, n (%)			
	Pirfenidone 2403 mg/d	Placebo	HR	p-value
All-cause mortality	27 (7.8)	34 (9.8)	0.77	0.315
IPF-related mortality	18 (5.2)	28 (8.1)	0.62	0.117
On-treatment				
All-cause mortality	19 (5.5)	29 (8.4)	0.65	0.141
IPF-related mortality	12 (3.5)	25 (7.2)	0.48	0.030

Summary of Efficacy (1)

- PIPF-004 demonstrated benefit on primary endpoint of change in %FVC at Wk 72
  - Clinically meaningful effect observed on categorical %FVC change and PFS
- PIPF-006 did not achieve primary endpoint of change in %FVC at Wk 72
  - Treatment effect on %FVC observed through Wk 48 and overall in repeated measures analysis
  - Clinically meaningful effect observed on 6MWT distance

Summary of Efficacy (2)

- Pooled analyses of PIPF-004 and PIPF-006
  - Provide most precise estimates of effect
  - Shows a clinically meaningful effect on %FVC, PFS, and 6MWT distance
- Dose-response supports overall efficacy findings and selection of pirfenidone 2403 mg/d dose

Overall Efficacy Conclusions

- Collective evidence from these studies, including the robust and statistically persuasive results in PIPF-004, demonstrate the clinically meaningful benefit of pirfenidone in patients suffering from IPF

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Unmet Medical Need	Ron du Bois, MD Professor of Medicine *National Jewish Health*
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Safety	**Steven Porter, MD, PhD**
Benefit / Risk	Paul Noble, MD, FCCP Professor of Medicine, Chief of Pulmonary, Allergy, & Critical Care Medicine *Duke University*

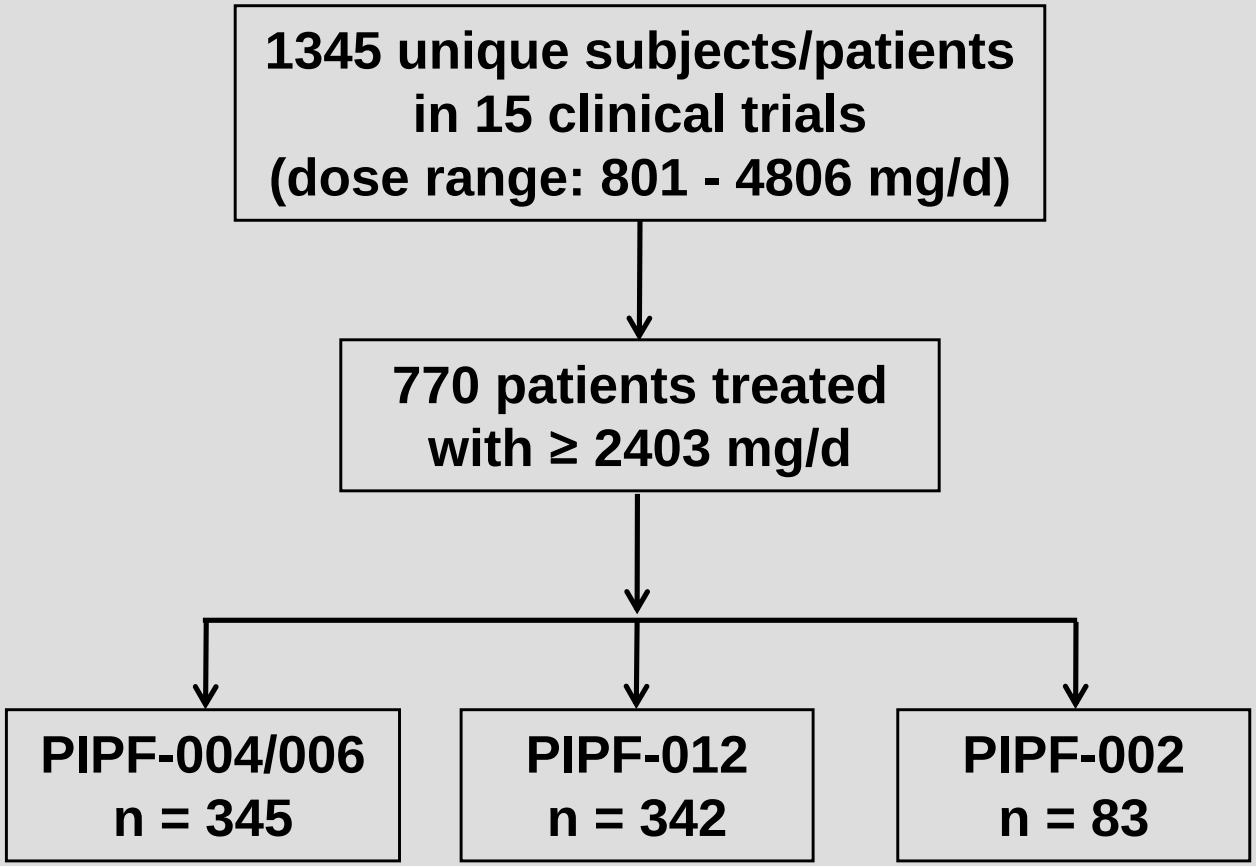
Safety of Pirfenidone

Steven Porter, MD, PhD

Chief Medical Officer & Sr VP Clinical Affairs

InterMune

Overall Exposure to Pirfenidone



Exposure to Pirfenidone in the 4 InterMune Phase 2 and 3 Clinical Trials

Treatment duration, mo	Patients, n (%)
≥ 12	436 (55.3)
≥ 24	280 (35.5)
≥ 36	31 (3.9)
≥ 48	9 (1.1)

Treatment-Emergent AEs

	Patients, %	
	Pirfenidone 2403 mg/d N = 345	Placebo N = 347
Adverse events	98.6	97.7
Serious AEs	32.8	31.4
AE leading to dose modification	46.4	18.4
AE leading to early D/C of treatment	14.8	8.6
On-treatment mortality	5.5	8.4

Most Common TEAEs With Higher Incidence in Pirfenidone Group*

Adverse event	Patients, %	
	Pirfenidone 2403 mg/d N = 345	Placebo N = 347
Nausea	36.2	17.3
Rash	32.2	11.5
Dyspepsia	19.1	7.5
Dizziness	18.3	10.1
Vomiting	13.6	4.3
Photosensitivity reaction	12.2	1.7
Anorexia	10.7	3.7
Arthralgia	10.4	6.9

*Occurring in ≥ 10% of pirfenidone 2403 mg patients and an incidence ≥ 1.5 × placebo.

TEAEs Leading to Treatment Discontinuation*

	Patients, %	
	Pirfenidone 2403 mg/d N = 345	Placebo N = 347
Any TEAE leading to D/C	14.8	8.6
Idiopathic pulmonary fibrosis	2.9	2.6
Rash	1.4	0
Nausea	1.4	0
Bladder cancer†	0.9	0
Photosensitivity reaction	0.9	0.3
Respiratory failure	0.9	0.3
Weight decrease	0.6	0

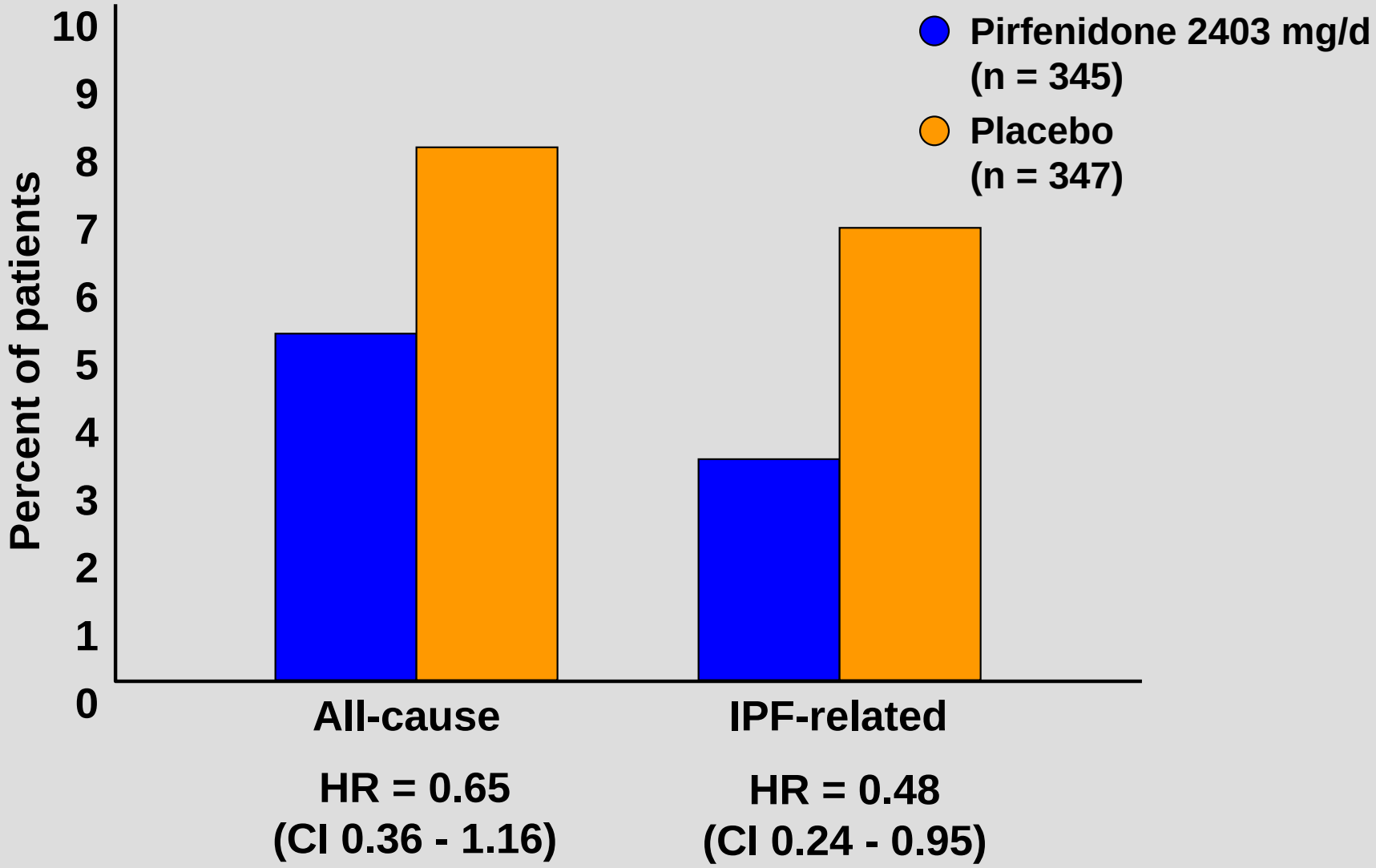
*Occurring in ≥ 2 patients in pooled pirfenidone 2403 mg/day group.
† Overall bladder cancer reported in 3 pirfenidone and 2 placebo patients.

Treatment-Emergent SAEs*

	Patients, %	
	Pirfenidone 2403 mg/d N = 345	Placebo N = 347
Any TE SAE	32.8	31.4
Coronary artery disease	1.7	0.6
Pneumothorax	1.2	0.3
Chest pain	1.2	0
Atrial fibrillation	0.9	0.6
Acute renal failure	0.9	0.6
Angina pectoris	0.9	0.6
Bladder cancer	0.9	0.3
Fall	0.9	0.3
Syncope	0.9	0.3

*Observed in ≥ 3 pts in pirfenidone group and with a higher incidence than placebo.

Incidence and Cause of On Treatment Death



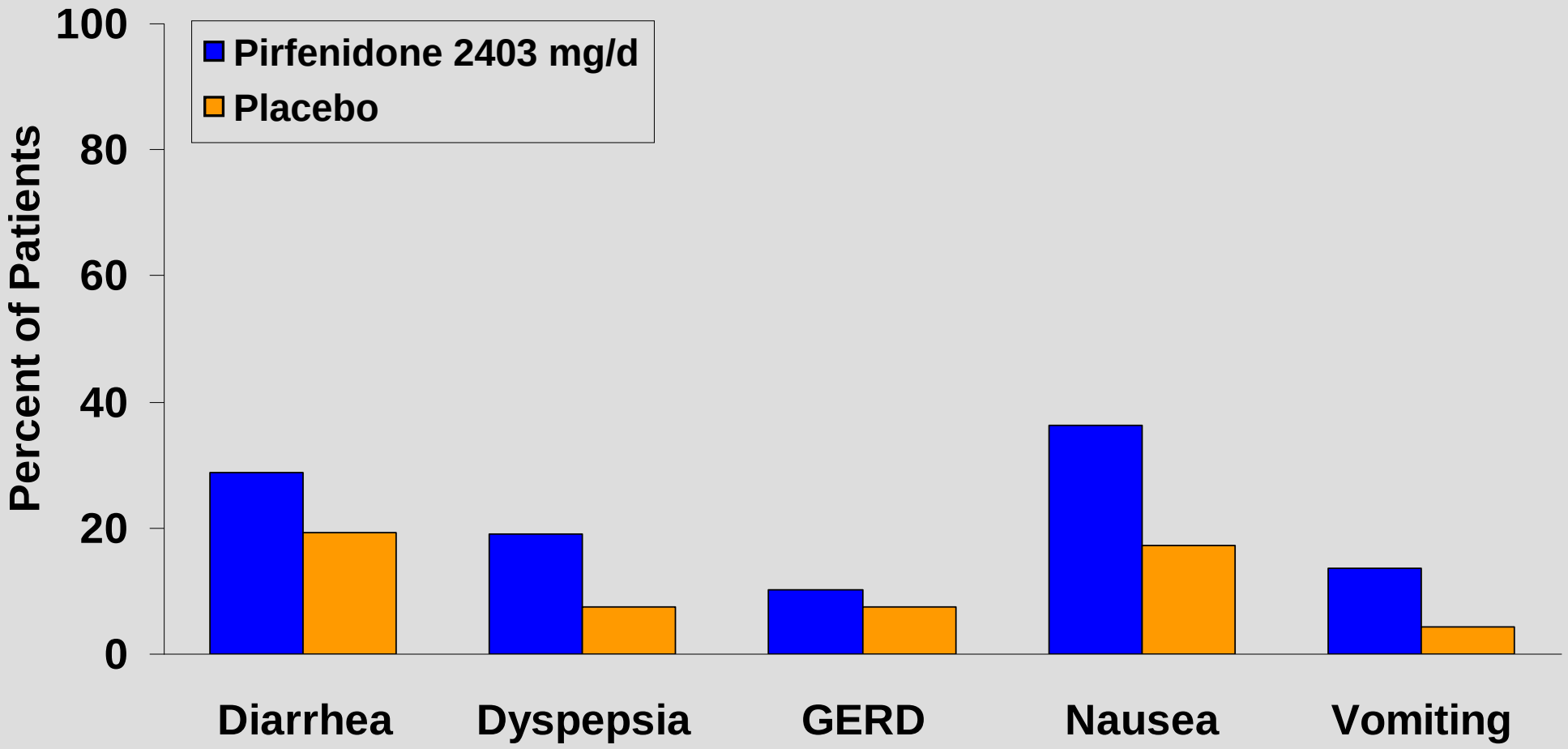
AEs of Interest

- Anorexia and Decreased Appetite
- Cardiac Disorders
- Dizziness
- Fatigue
- Gastrointestinal Events
- Hepatic Events
- Hyponatremia
- Injury Events
- Photosensitivity Reactions and Rash
- Weight Loss

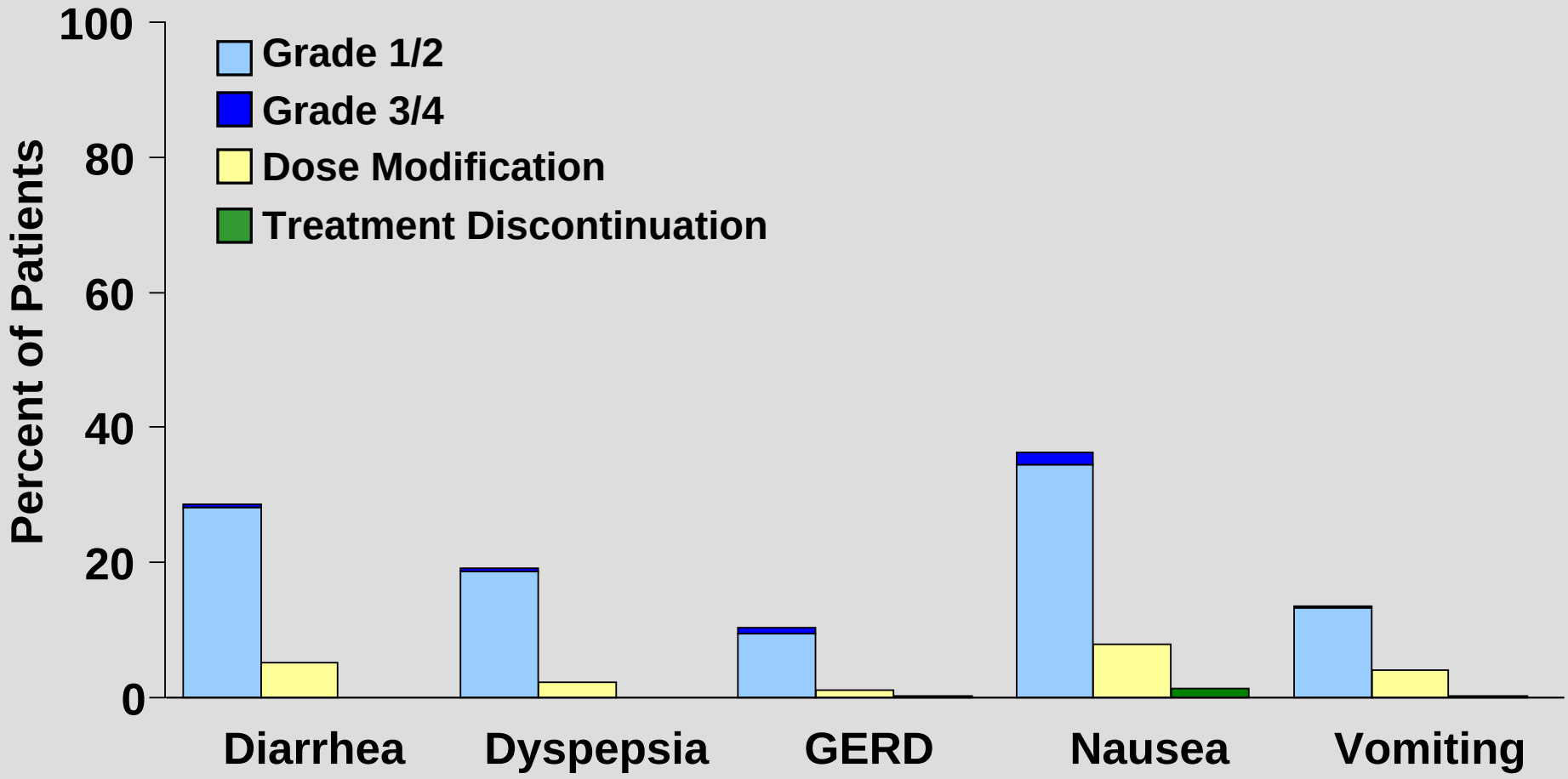
AEs of Interest

- Anorexia and Decreased Appetite
- Cardiac Disorders
- Dizziness
- Fatigue
- **Gastrointestinal Events**
- **Hepatic Events**
- Hyponatremia
- Injury Events
- **Photosensitivity Reactions and Rash**
- Weight Loss

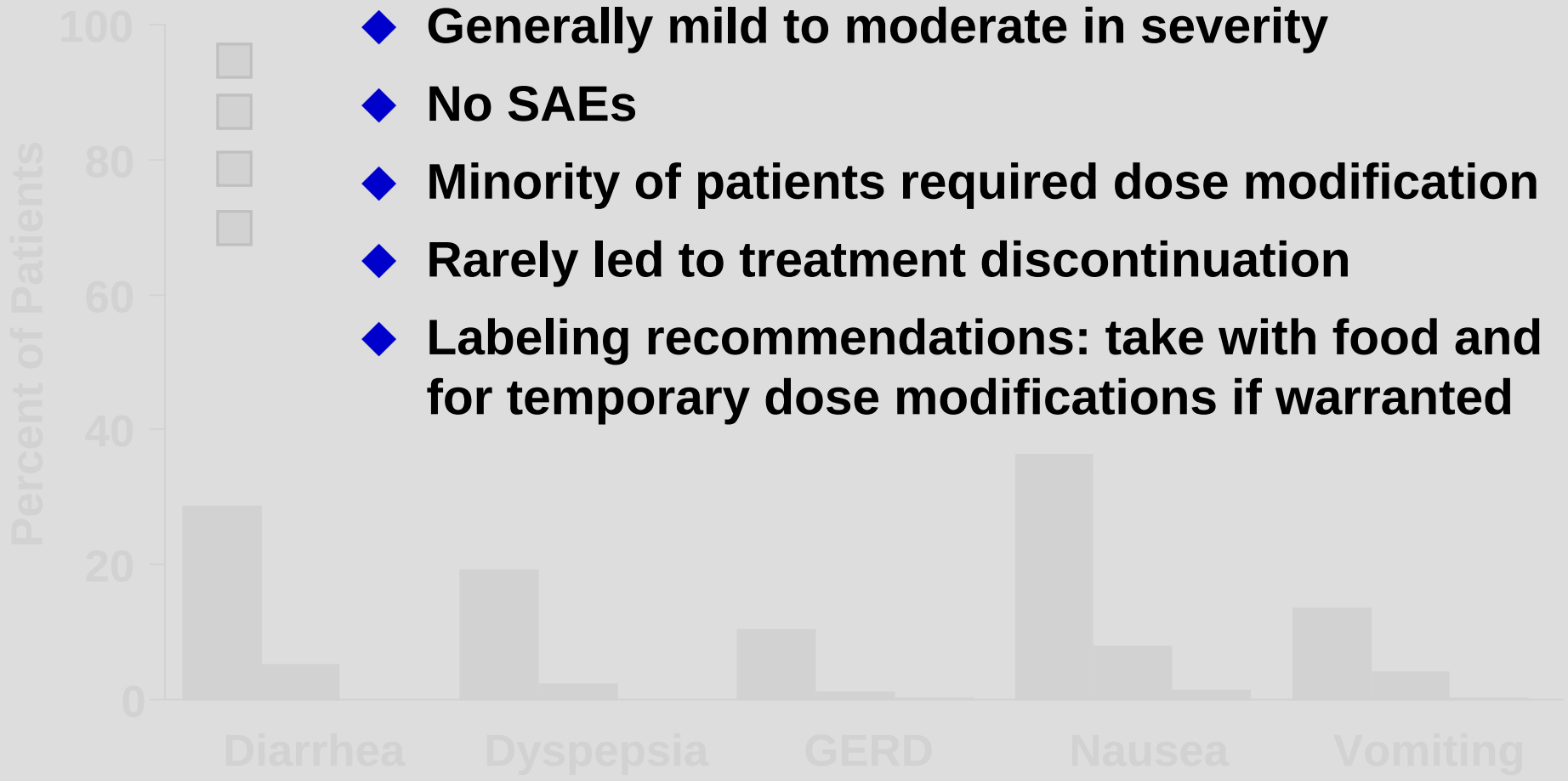
Gastrointestinal AEs



Gastrointestinal AEs – Pirfendone 2403 mg/d

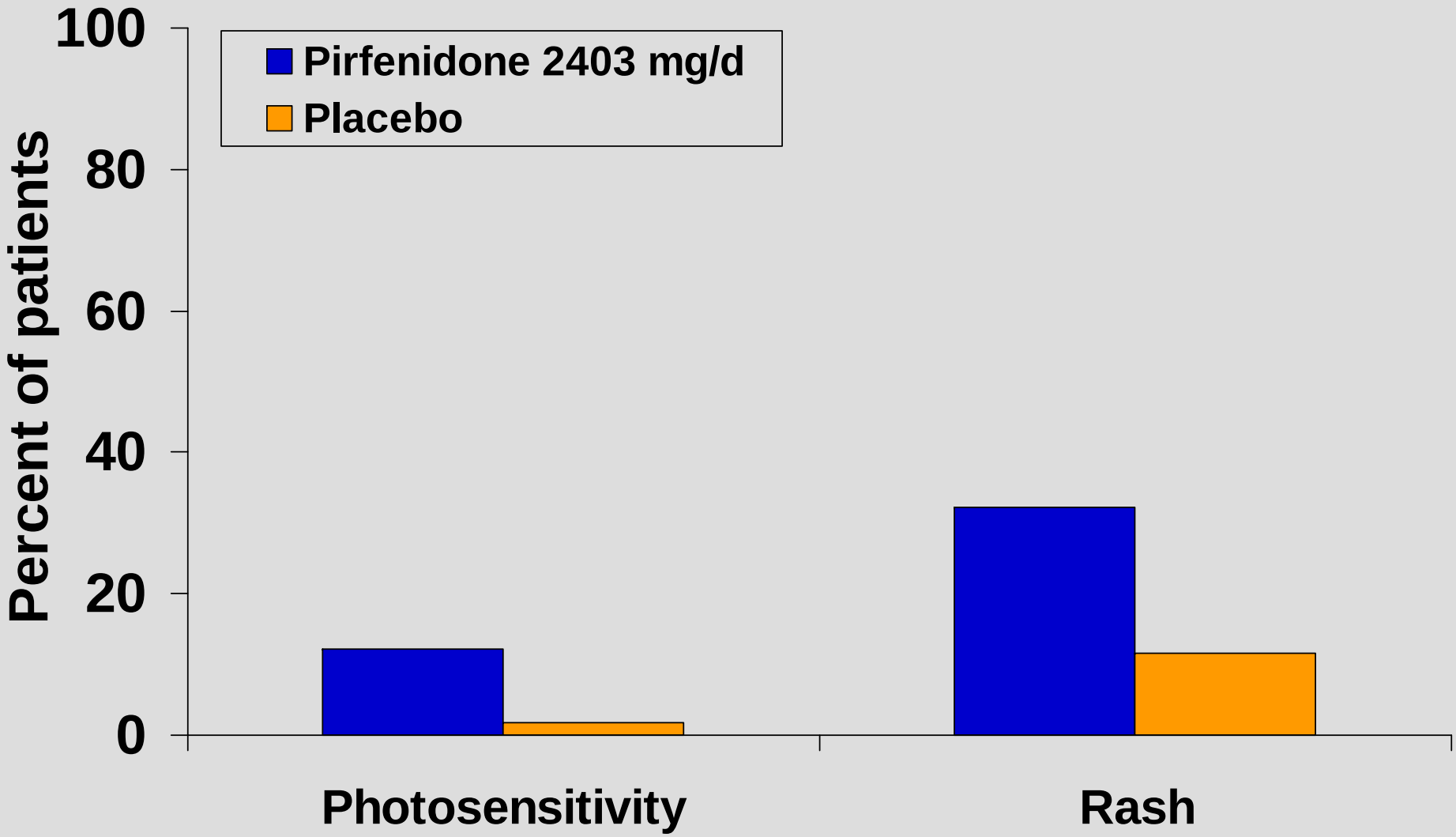


Gastrointestinal AEs – Summary

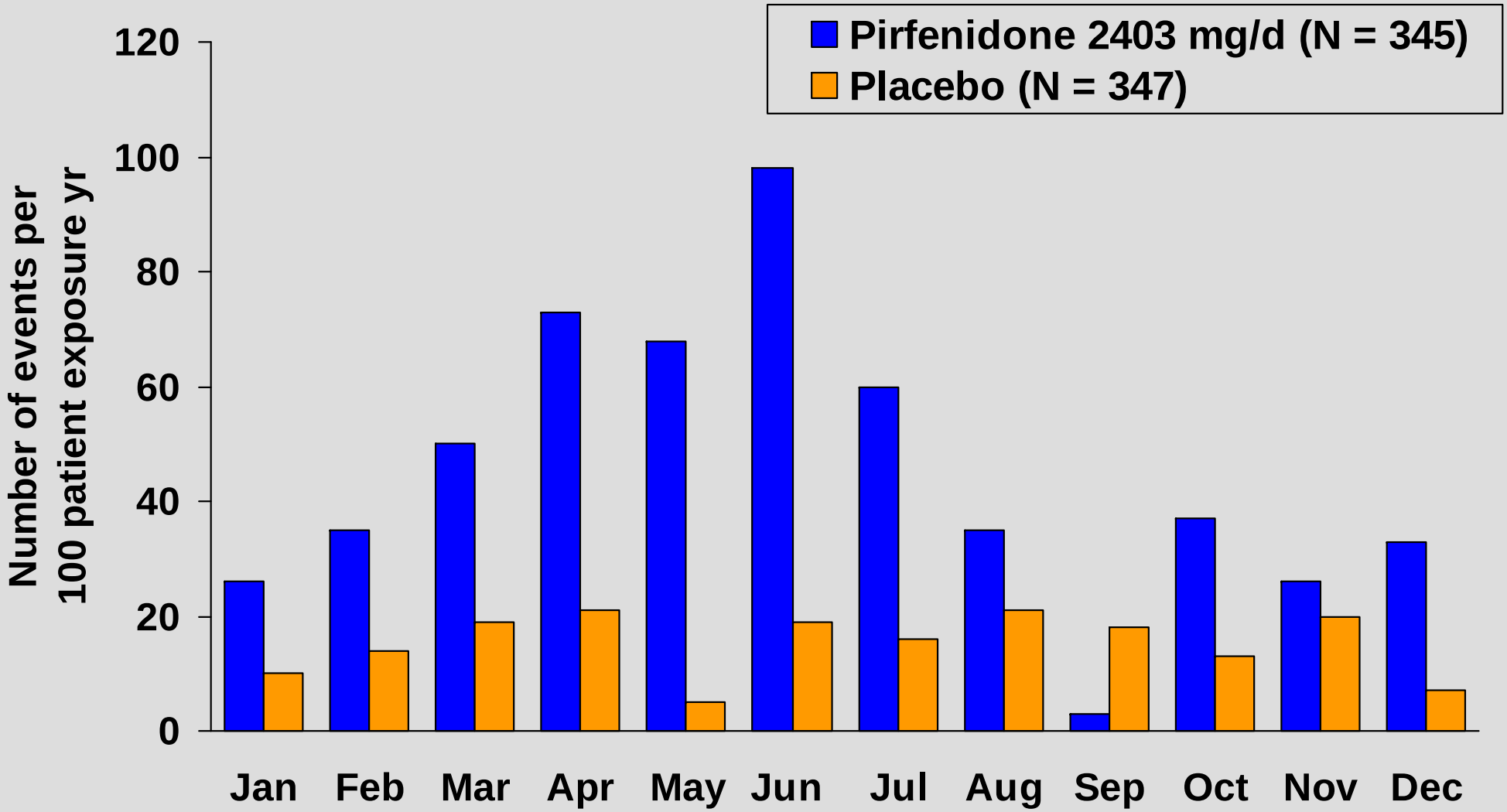


- Generally mild to moderate in severity
- No SAEs
- Minority of patients required dose modification
- Rarely led to treatment discontinuation
- Labeling recommendations: take with food and for temporary dose modifications if warranted

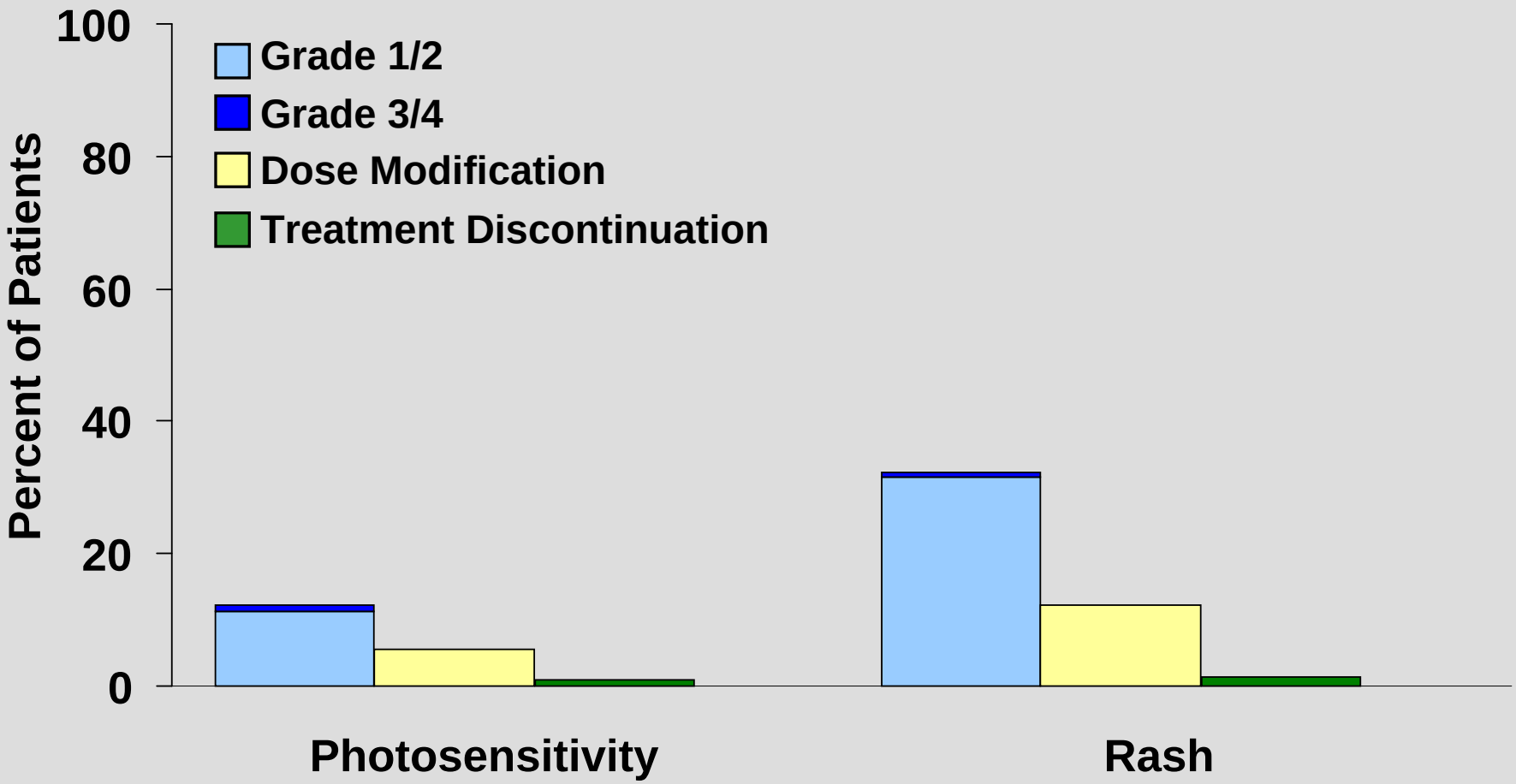
Rash and Photosensitivity AEs



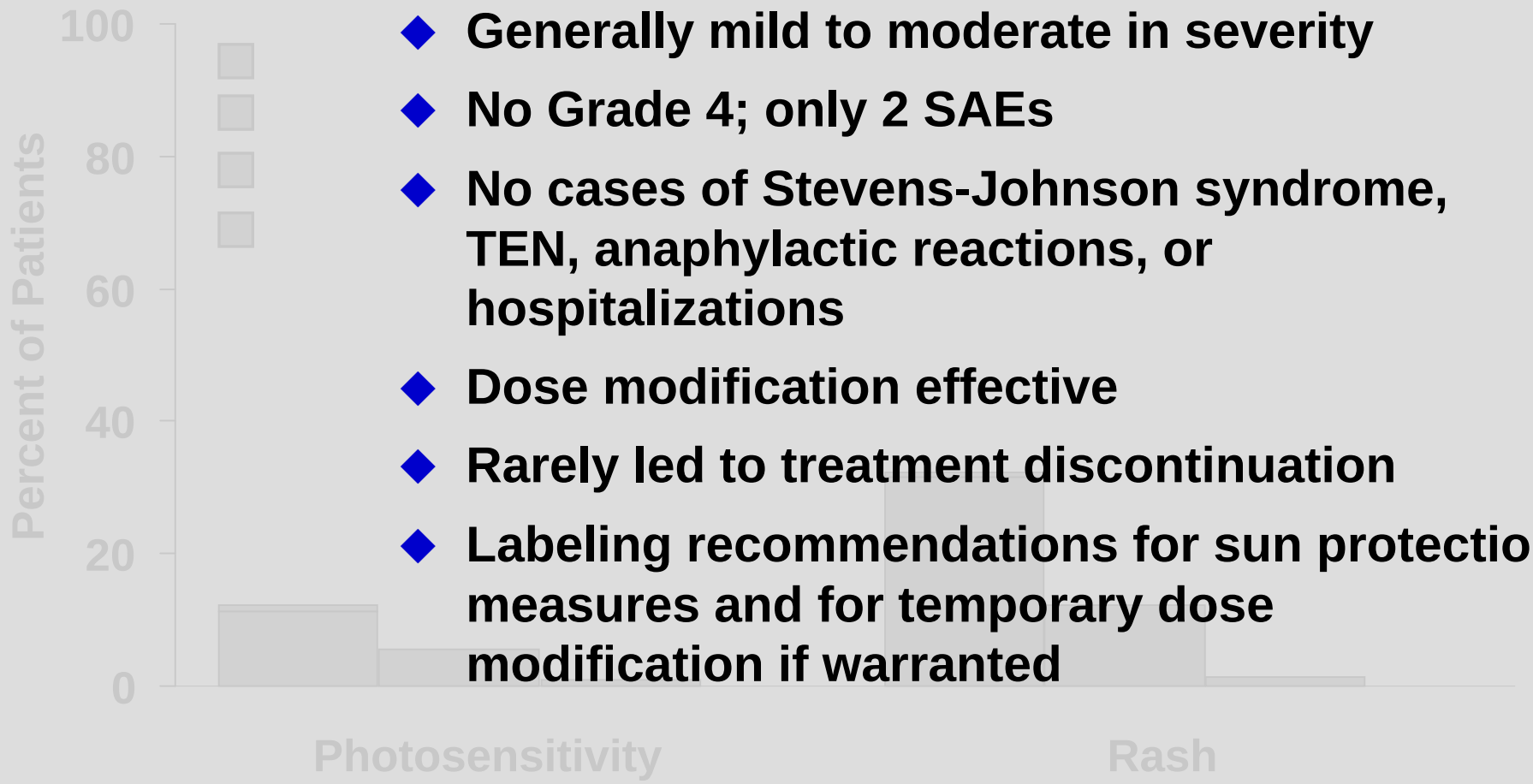
Rash and Photosensitivity Incidence by Month



Rash and Photosensitivity Reaction AEs – Pirfenidone 2403 mg/d



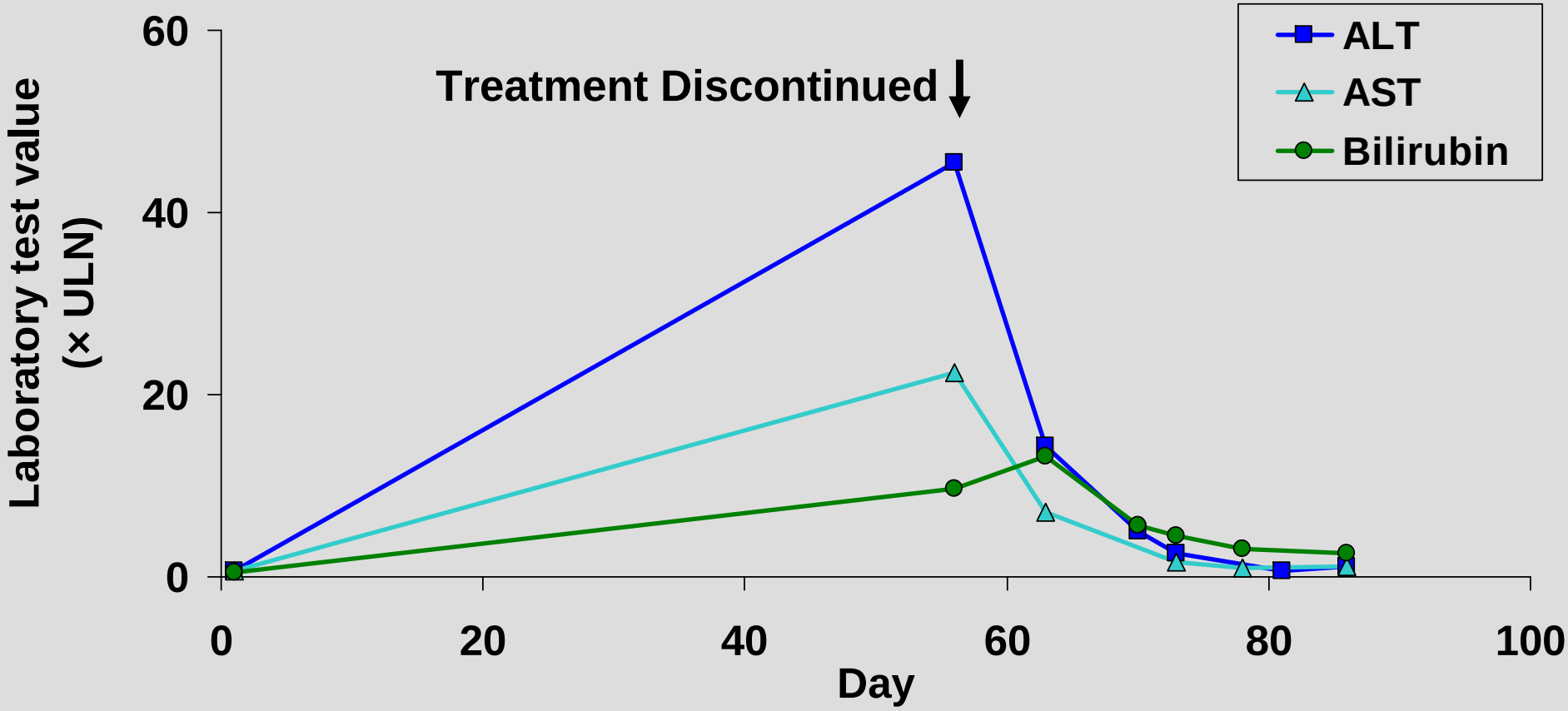
Rash and Photosensitivity Reaction AEs – Summary



- Generally mild to moderate in severity
- No Grade 4; only 2 SAEs
- No cases of Stevens-Johnson syndrome, TEN, anaphylactic reactions, or hospitalizations
- Dose modification effective
- Rarely led to treatment discontinuation
- Labeling recommendations for sun protection measures and for temporary dose modification if warranted

One Case Meeting Criteria for Hy's Law in Safety Database

- Shionogi Phase 2 Patient SP2-02-04 (1800 mg/d)

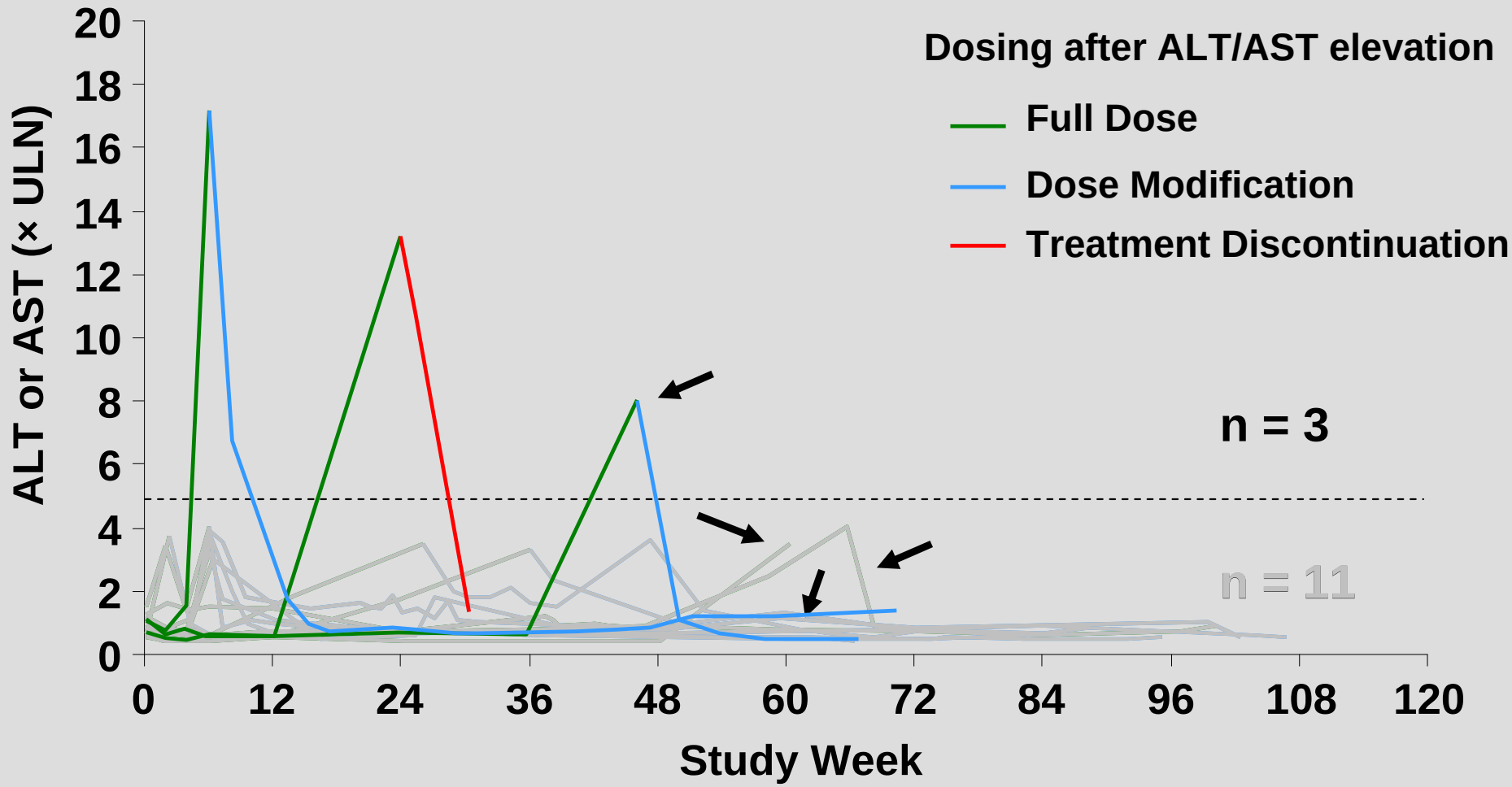


Liver Enzyme Elevations

	Patients, %	
	Pirfenidone 2403 mg/d N = 345	Placebo N = 347
ALT or AST increased		
> 3× ULN	4.1	0.6
> 5× ULN	0.9	0.6
≥ 10× ULN	0.3	0.3
≥ 20× ULN	0	0.3
Total serum bilirubin > 2× ULN	0	0
Liver-related TE SAE*	0.9	0.3
Liver-related deaths	0	0
Hy's Law	0	0
Dose modifications due to ALT/AST elevations	3.5	0.3
Discontinuations due to ALT/AST elevations	0.6	0.3

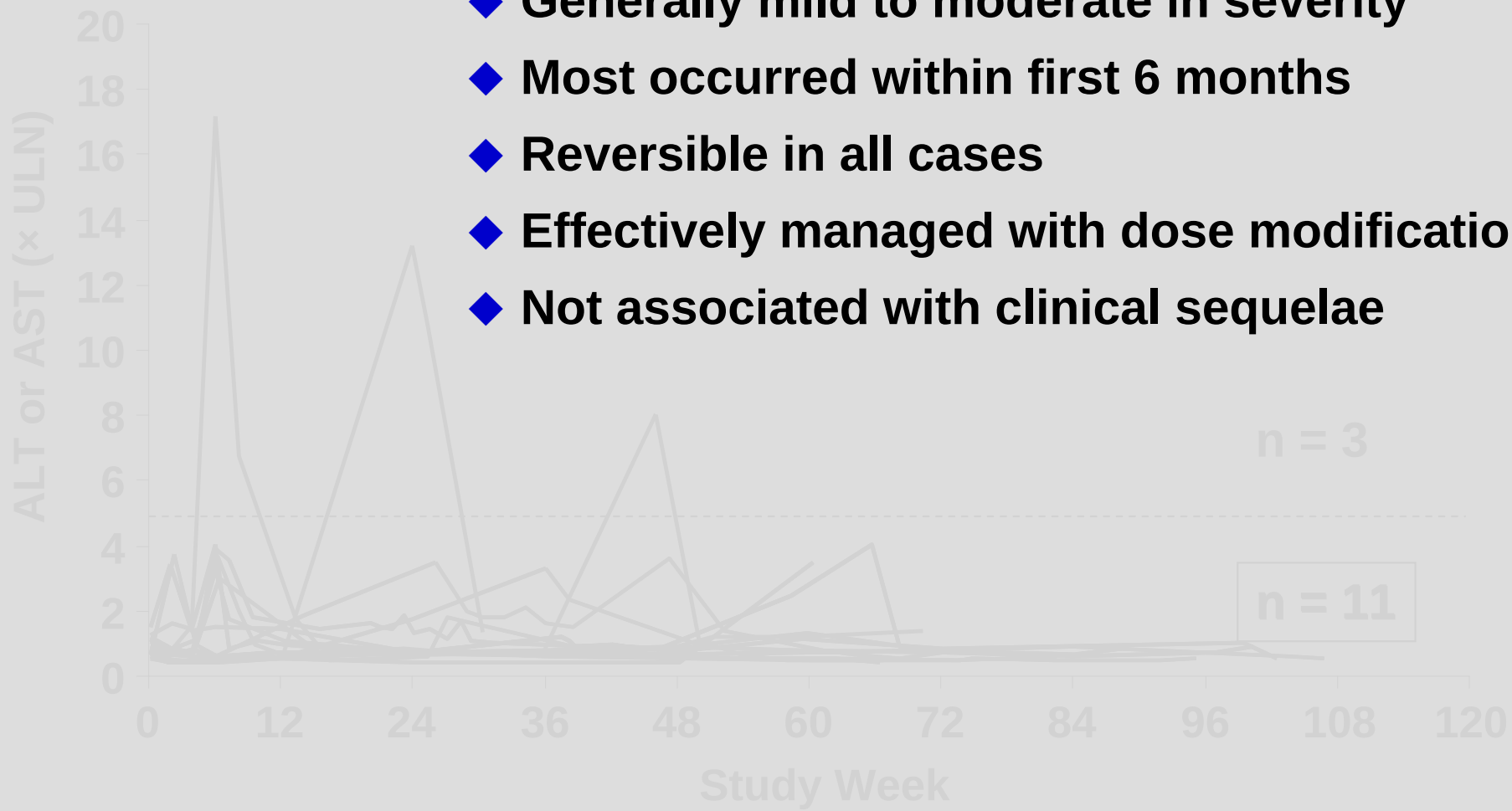
*ALT or AST increased; LFT abnormal; hepatitis.

Liver Enzyme Elevations – Patient Profiles



Liver Enzyme Elevations – Patient Profiles

- Generally mild to moderate in severity
- Most occurred within first 6 months
- Reversible in all cases
- Effectively managed with dose modification
- Not associated with clinical sequelae



Proposed Labeling for LFT Management

LFT Monitoring

- Liver enzymes should be measured prior to initiation of therapy in all patients, then monthly for first 6 months and every 3 months thereafter
- Patients should be instructed to report symptoms of liver disease (eg., dark urine and/or jaundice) to their physician

Dose Modification

- > 3 to 5× ULN aminotransferase elevation
  - Confounding medications should be discontinued and patient monitored closely. Daily dose may be maintained at full dose if clinically appropriate, or reduced or interrupted (eg., until liver function tests are within normal limits) with subsequent re-escalation to full dose as tolerated
- > 5× ULN aminotransferase elevation or ≤ 5× ULN aminotransferase elevation accompanied by symptoms or hyperbilirubinemia
  - Treatment should be permanently discontinued

Safety Summary—Other Studies

- SP3
  - Consistent with the PIPF-004/006 safety profile
- Long-term safety studies (PIPF-002/012)
  - Consistent with the PIPF-004/006 safety profile
  - Up to 72 months of follow-up
- Post-marketing experience in Japan
  - ~ 1400 patients
  - No new safety signals

Sponsor-Proposed Risk Evaluation & Mitigation Strategy (REMS)

- Goals
  - Encourage informed benefit-risk decisions
  - Minimize potential risk of hepatotoxicity and photosensitivity reaction or rash
- REMS Elements
  - Patient Medication Guide
  - Healthcare Provider Communication Plan
  - Recommendations for liver function monitoring and sun-protection measures
- Closed distribution network via specialty pharmacy providers due to small numbers of patients

Overall Safety Conclusions

- Favorable safety profile
- Similar incidence of SAEs and fewer deaths observed in pirfenidone group relative to placebo group
- AEs are primarily manageable tolerability issues
  - Majority of AEs were mild or moderate
  - GI and photosensitivity/rash more common in pirfenidone group – few treatment discontinuations
  - Small imbalance in transaminase elevations
    - Readily monitored and reversible
    - Managed with dose modification
- Consistent long-term safety and post-marketing experience
- AEs managed through labeling and REMS

Agenda

Introduction	**Steven Porter, MD, PhD** Chief Medical Officer & Sr. VP Clinical Affairs *InterMune*
Unmet Medical Need	**Ron du Bois, MD** Professor of Medicine *National Jewish Health*
Efficacy	**Bill Bradford, MD, PhD** Sr. VP, Clinical Sciences & Biometrics *InterMune*
Safety	**Steven Porter, MD, PhD**
Benefit / Risk	**Paul Noble, MD, FCCP** **Professor of Medicine, Chief of Pulmonary, Allergy, & Critical Care Medicine** ***Duke University***

Benefit Risk

Paul Noble, MD, FCCP

Professor of Medicine,
Chief of Pulmonary, Allergy,
& Critical Care Medicine
Duke University Medical Center

Unmet Medical Need

- Prognosis for IPF is dismal
  - Debilitating disease
  - Unrelenting breathlessness and irreversible loss of lung function
  - Median survival of 2 - 5 yrs
- Patient perspective of IPF
  - Diagnosis of IPF is a death sentence
  - No standard of care
  - Current treatments unproven and have significant toxicities

Challenge of Developing Therapies

- Complex and poorly understood disease
- Nature of disease progression
  - Heterogeneous, inevitable but unpredictable progression
- Limited experience to guide IPF trial design
  - Recent 600+ / 4-yr patient trial failed
- Positive phase 3 trials represent pioneering work

Clinical Benefits of Pirfenidone on Lung Function

- PIPF-004 and PIPF-006 were well-conducted studies
- PIPF-004 showed a clear and durable impact on the decline in FVC, improved progression-free survival and reduced categorical decline in FVC of ≥ 10%
- PIPF-006 results were not identical, but similar effects on FVC were seen through 48 wks of study
- Shionogi Phase 3 trial showed a similar effect on VC and PFS through 52 wks

Observed Effect on Percent Predicted FVC Change is Clinically Meaningful

- Primary efficacy analysis demonstrated a clear and convincing treatment effect
  - This result reflects the treatment effect across the entire IPF study population
- The clinical benefit to individual patients is best assessed in categorical changes in FVC
  - Pirfenidone significantly reduced number of patients who experienced the most substantial loss of lung function
  - Pirfenidone increased the number of patients whose lung function did not decline
- FVC matters in IPF

Meaningful and Consistent Magnitude of Pirfenidone Effect on Supportive Measures

Outcome	Incidence, %		
	Pirfenidone 2403 mg/d N = 345	Placebo N = 347	Risk estimate (95% CI)
%FVC decrease ≥ 10%[1-3]	21.4	30.5	0.70 (0.54 - 0.91)
6MWT distance decrease ≥ 50 m[4-6]	34.8	47.0	0.74 (0.62 - 0.89)
Progression free survival	28.9	35.4	0.74 (0.57 - 0.96)
Overall survival	7.8	9.8	0.77 (0.47 - 1.28)

1 Collard H. *Am J Respir Crit Care Med* 2003 ;168:538–542.
2 Flaherty K. *Am J Respir Crit Care Med* 2003;168:543–548.
3 King T. *Chest;* 2005127:171–177.
4 Caminati A. *Respir Med.* 2009;103:117-123.
5 Hallstrand T. *Eur Respir J.* 2005;*25:96-103.*
6 Lederer D. *Am J Respir Crit Care Med.* 2006;*174:659-664.*

Risk Profile

- Safety profile is well characterized
- Primarily issues of tolerability, not morbidity
- AEs readily monitored and reversible
  - Common AEs are GI symptoms and photosensitivity/rash, but few lead to treatment discontinuations
  - Aminotransferase elevations in small proportion of patients
- IPF patients have frequent follow-up visits with pulmonologists

Benefit Risk Summary

- Patients with IPF suffer from a fatal disease with no treatment options
- Totality of the clinical data demonstrates clear treatment effect
  - Preventing loss of lung function in an irreversible disease is clinically meaningful
- Risks are manageable and acceptable
- Pirfenidone is an important first step in IPF treatment
  - First drug to have a favorable benefit-risk profile

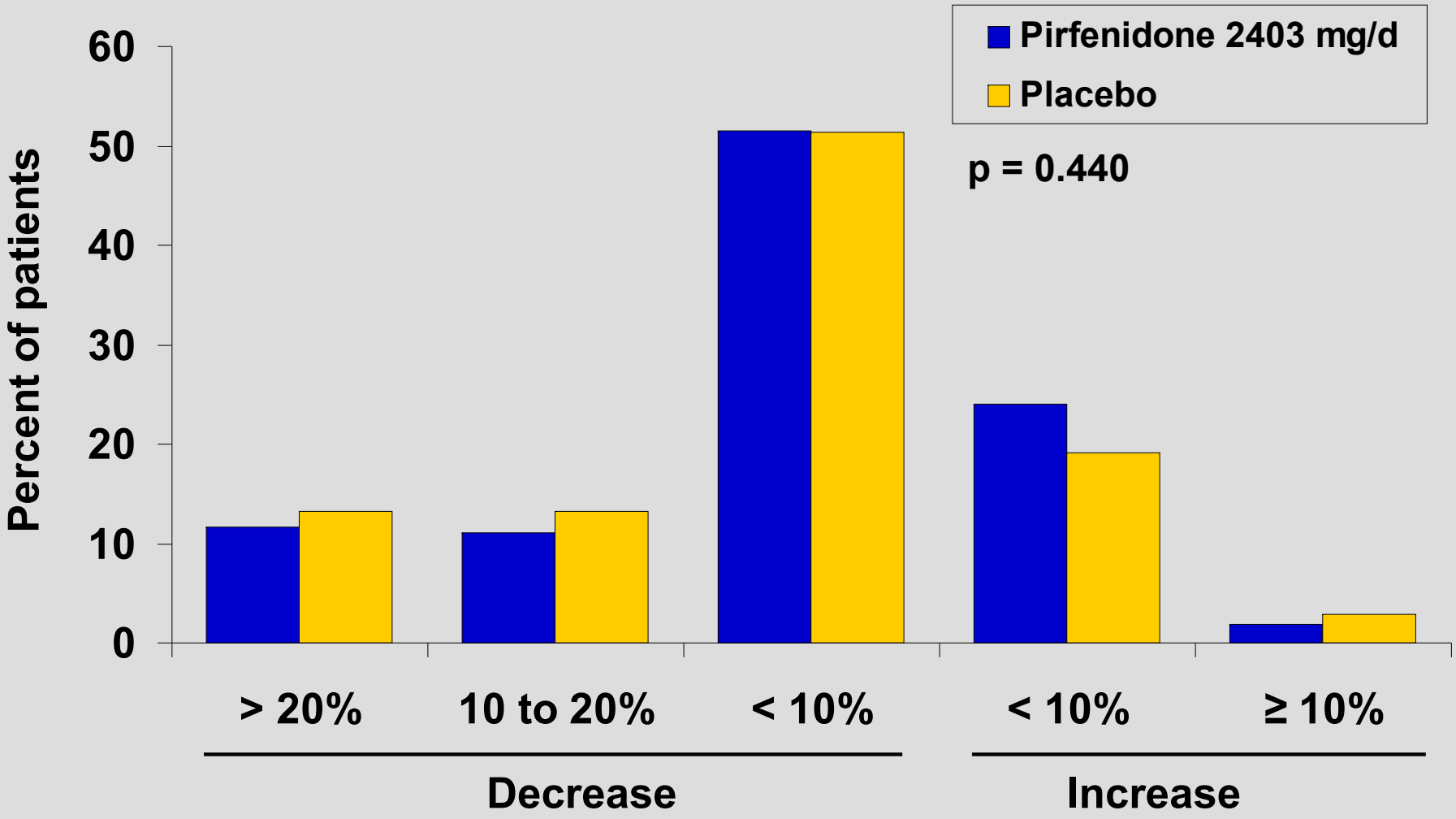
Pirfenidone
NDA 22-535

Pulmonary-Allergy Drugs Advisory Committee

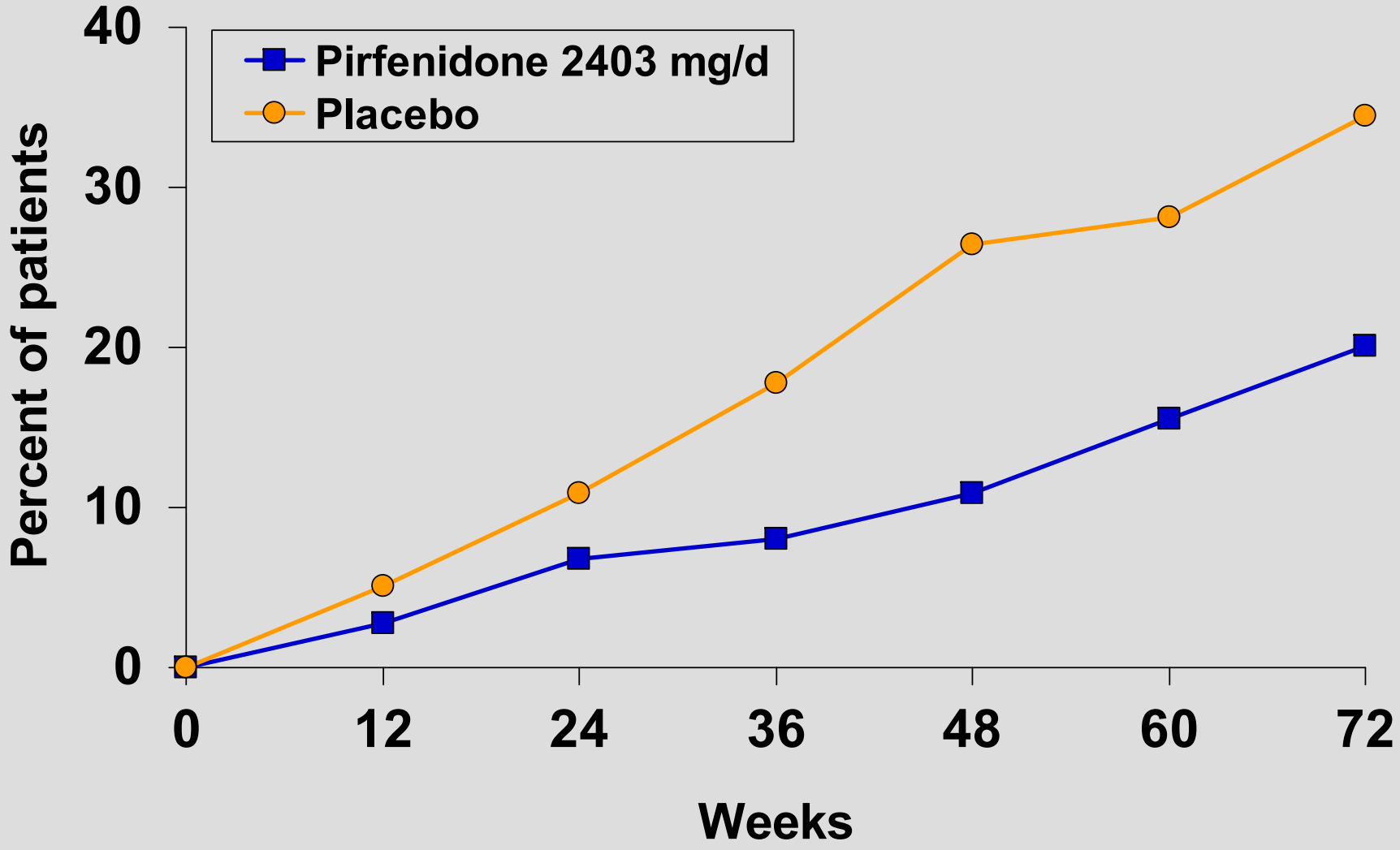
March 9, 2010

Support slides

Categorical Assessment of Change in Percent Predicted FVC at Wk 72
PIPF-006



Decrease from Baseline of ≥ 10% in %FVC
PIPF-004

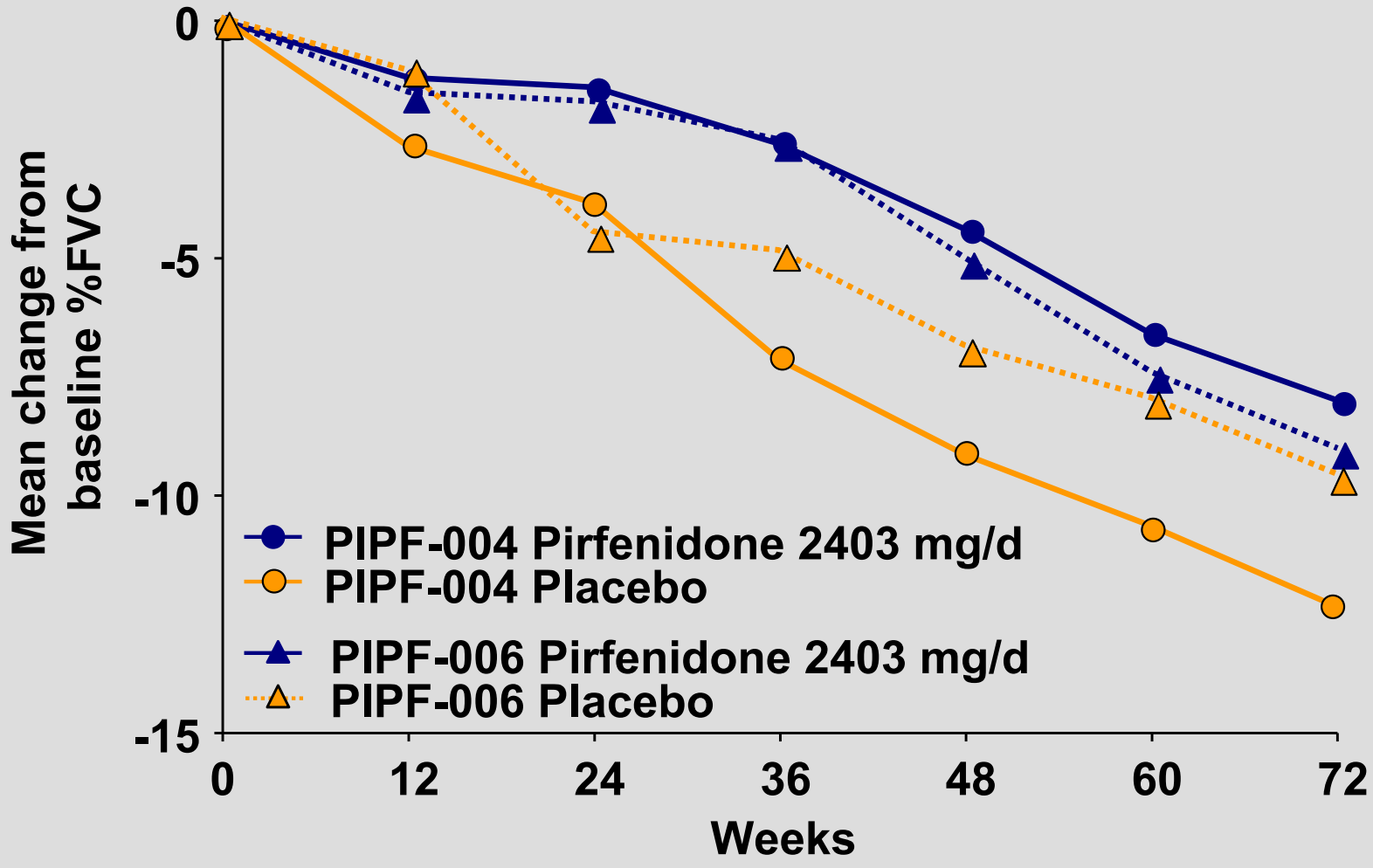


Post-hoc Categorical Analysis Change in UCSD SOBQ Pooled PIPF-004 and PIPF-006

UCSD SOBQ Score	Patients, n (%) Pirfenidone 2403 mg/d n = 274	Placebo n = 257	p-value*
Increase of ≥ 25	71 (20.9)	90 (26.5)	0.091
Increase of < 25	268 (79.1)	250 (73.5)	

UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire
p-value from CMH test

Change in %FVC Over Time
PIPF-004 and PIPF-006

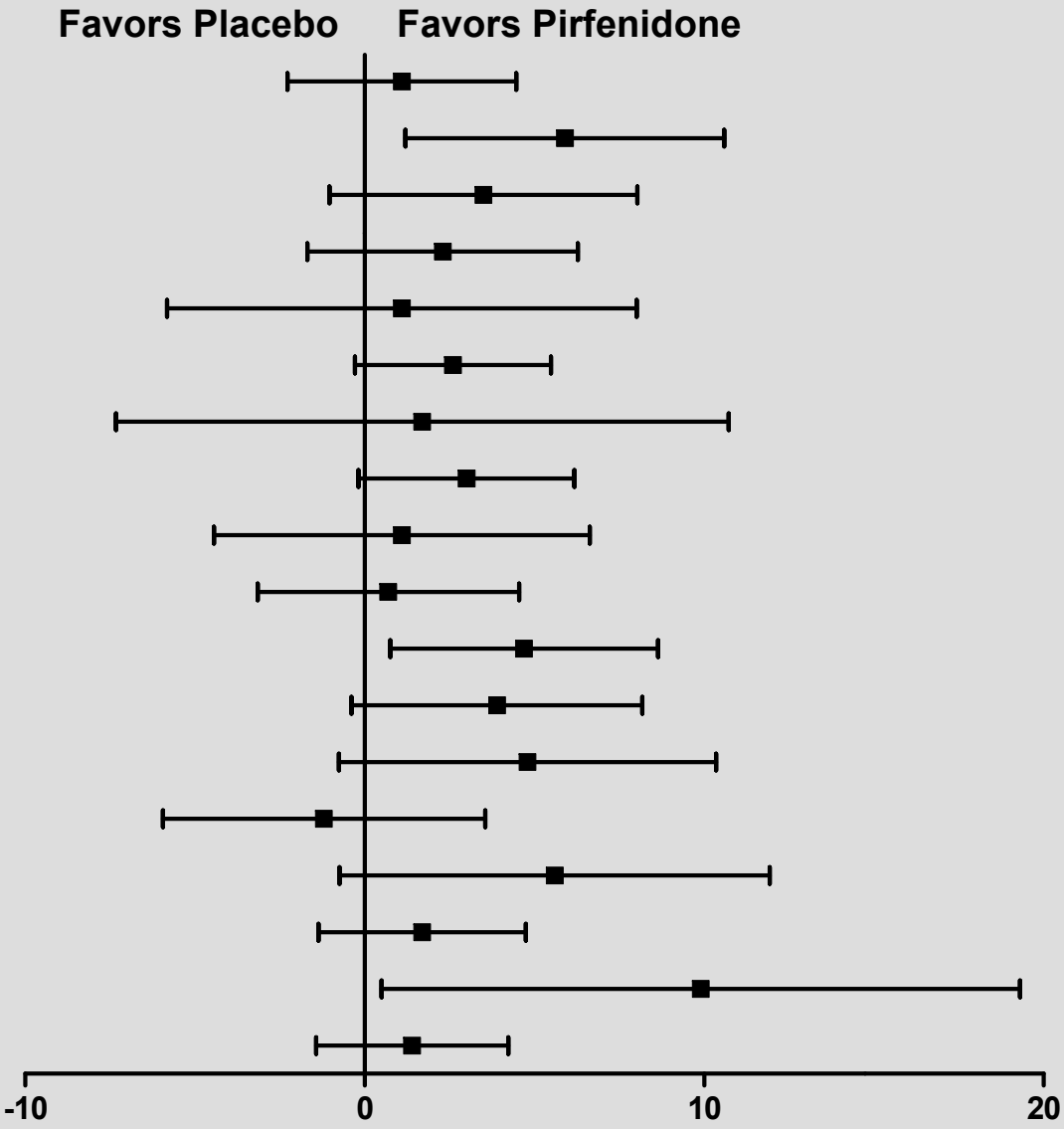


Clinical Sites and Number of Patients by Country
PIPF-004 and PIPF-006

	PIPF-004		PIPF-006		Total	
	# Sites	# Patients	# Sites	# Patients	# Sites	# Patients
USA	33	286	31	298	64	584
Canada	9	47	-	-	9	47
Italy	9	47	-	-	9	47
Germany	-	-	6	21	6	21
France	5	18	-	-	5	18
Spain	-	-	4	15	4	15
UK	3	13	-	-	3	13
Poland	2	12	-	-	2	12
Australia	2	9	1	1	3	10
Belgium	-	-	2	7	2	7
Mexico	1	3	-	-	1	3
Ireland	-	-	1	1	1	1
Switzerland	-	-	1	1	1	1

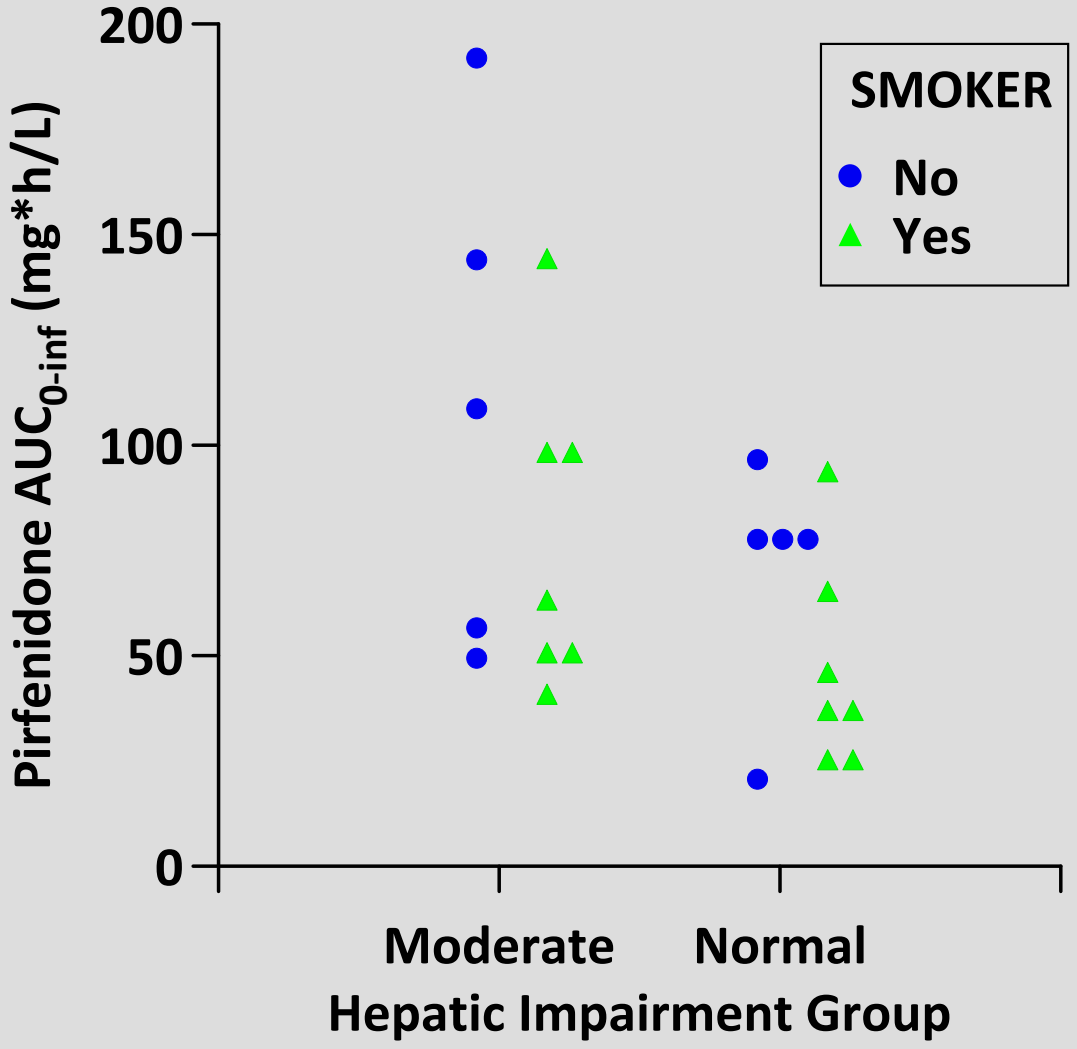
No site in either study enrolled ≥ 8% of patients.

Subgroup Analyses of Wk 72 %FVC Change
Pooled PIPF-004 and PIPF-006

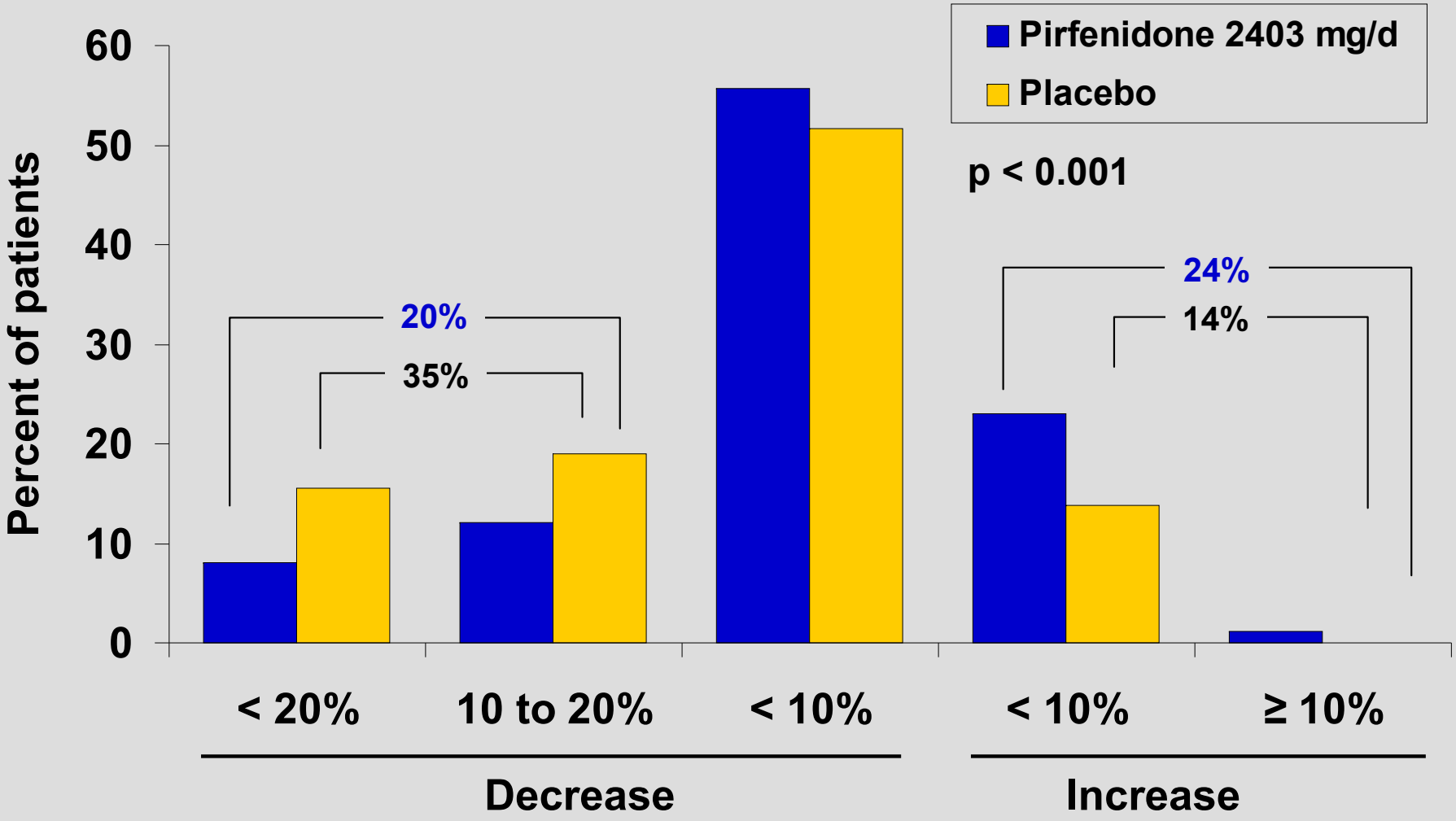


* Significant interaction with treatment.

PIPF-011 – Influence of Hepatic Impairment on PK

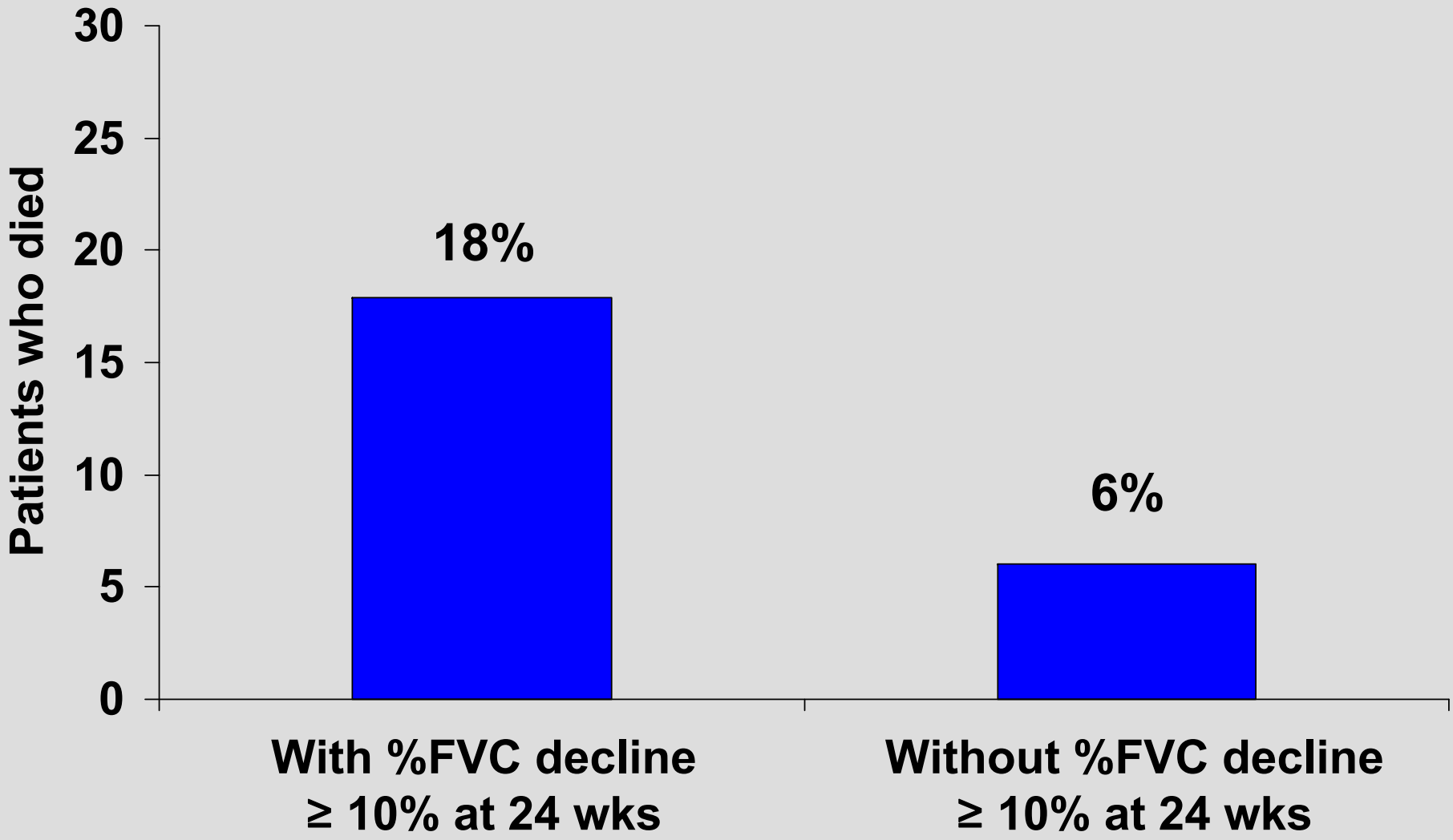


Categorical Assessment of Change in %FVC at Wk 72
PIPF-004



Mortality Subsequent to ≥10 Decline in %FVC at Wk 24: Placebo Patients

Pooled PIPF-004 and PIPF-006



Baseline Characteristics (1)
PIPF-004 and PIPF-006

	PIPF-004			PIPF-006	
	Pirfenidone 1197 mg/d N = 87	Pirfenidone 2403 mg/d N = 174	Placebo N = 174	Pirfenidone 2403 mg/d N = 171	Placebo N = 173
Mean age, yrs	68	66	66	67	67
Male sex, %	75	68	74	72	72
Geographic region, %					
USA	67	66	66	87	87
ROW	33	35	35	14	13
Race, white	95	97	97	99	99
Supplemental O_2 use, %	17	17	14	28	28
Current or former smoker, %	69	68	71	66	63
Mean weight (kg)					
Male	88	91	89	95	93
Female	73	77	77	77	78
Mean BMI, kg/m^2					
Male	29	30	30	31	30
Female	29	31	30	31	30

Liver Tumors Summary

Preclinical

- Increased number of liver tumors in rodents (adenomas, blastomas, adenocarcinomas)
- Species-specific phenobarbital-like effect due to CYP induction (CYP2B)
  - Increased cell proliferation, hypertrophy and development of altered hepatic foci
  - Liver tumors in rodents through phenobarbital-like effects are not considered to be of human relevance (Holsapple et al. 2006)

Clinical

- No cases of primary liver carcinoma in ITMN studies
- 1 hepatoma (SP2) and 1 hepatic hemangioma (SP3)
- 1 liver cancer in Shionogi post-marketing

Cardiac Arrhythmia TEAEs*

Adverse event	Patients, %		
	Pirfenidone		Placebo
	1197 mg/d N = 87	2403 mg/d N = 345	N = 347
Arrhythmia	0	1.4	0
Atrial fibrillation	6.9	2.0	1.2
Bradycardia	1.1	1.7	0.6
Right BBB	1.1	0.9	0.3
QT prolongation	0	0.9	0.6
Increased HR	0	1.4	0.3
Palpitations	3.4	2.3	0.9
Sick sinus syndrome	1.1	0.9	0
Supraventricular tachycardia	2.3	0.9	0
Tachycardia	4.6	1.7	1.4

*TEAEs in ≥ 3 patients in either pirfenidone group and at higher incidence than placebo.

Baseline Differences Across Studies
PIPF-004 and PIPF-006

	Patients, n (%)			
	PIPF-004		PIPF-006	
	Pirfenidone 2403 mg/d n = 174	Placebo n = 174	Pirfenidone 2403 mg/d n = 171	Placebo n = 173
Diagnosis of IPF < 1 yr	48	47	59	62
Supplemental O_2 use	17	14	28	28
O_2 use during 6MWT	10	11	15	16
Resides within US	66	66	87	87

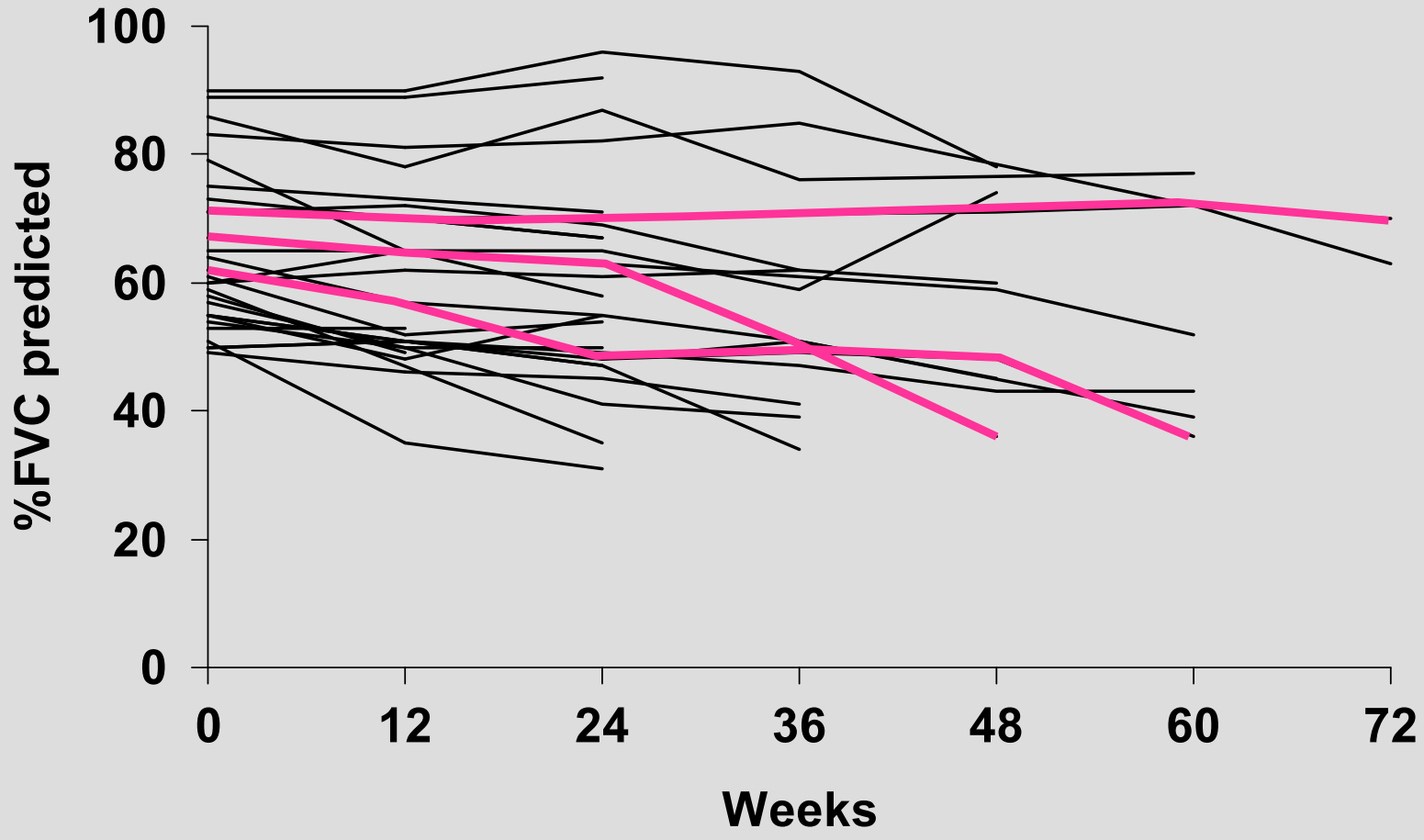
Analysis of Mean Change in %FVC at Wk 72 by Mean Daily Dose
Pooled PIPF-004 and PIPF-006

	Mean daily dose of study drug, mg/d		
	< 1602	1602-2300	>2300
Placebo			
Mean change in % FVC	-20.5	-12.7	-7.6
Patients, n	29	155	163
Pirfenidone 2403 mg/d			
Mean change in % FVC	-17.5	-6.5	-5.0
Patients, n	77	154	114
Difference in mean change, %	3.0	6.2	2.6

- ***A treatment effect of pirfenidone is evident in all 3 strata of mean daily dose***

Variable Clinical Course in IPF: Heterogeneity

- Heterogeneous disease progression
  - Considerable inter- and intra-patient variability
  - Many patients do not progress over a 1-yr period

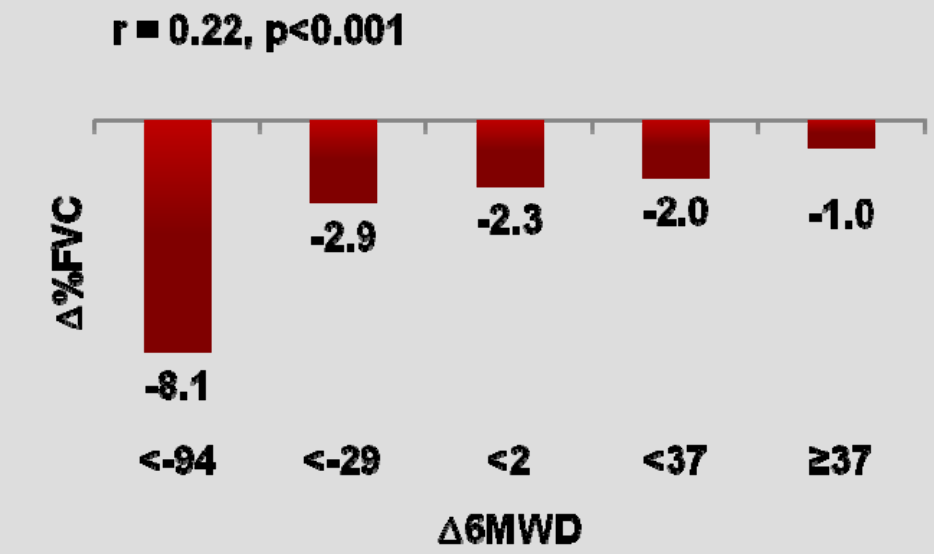


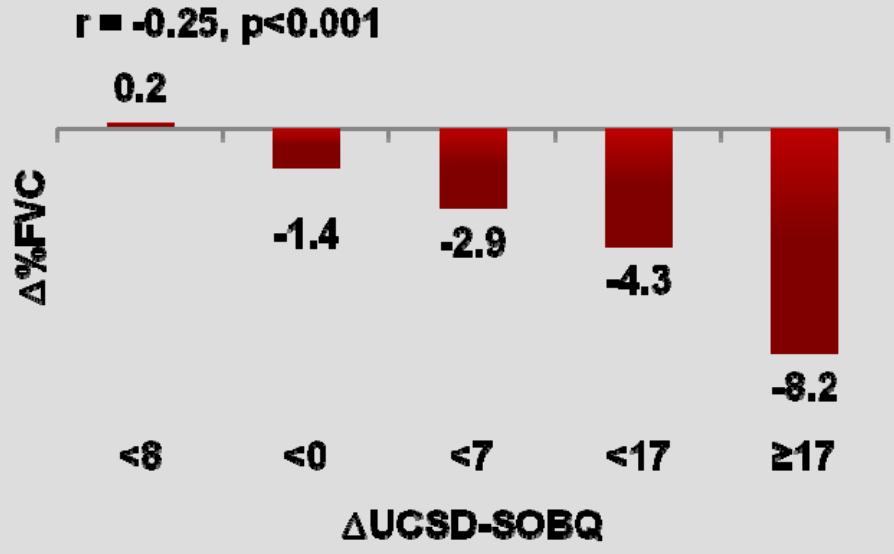
Martinez FJ, et al. Ann Int Med. 2005;142:963-967.

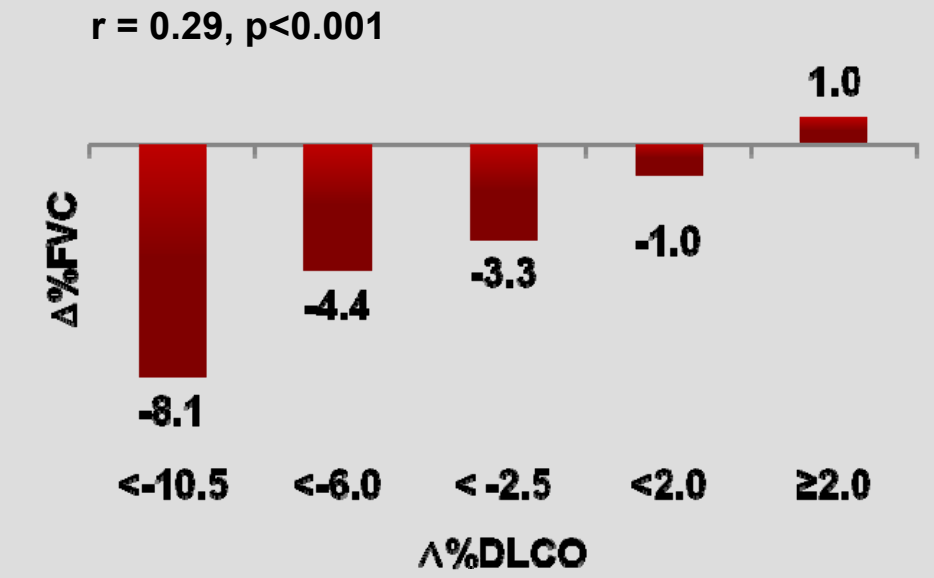
%FVC is Stable in Repeated Testing

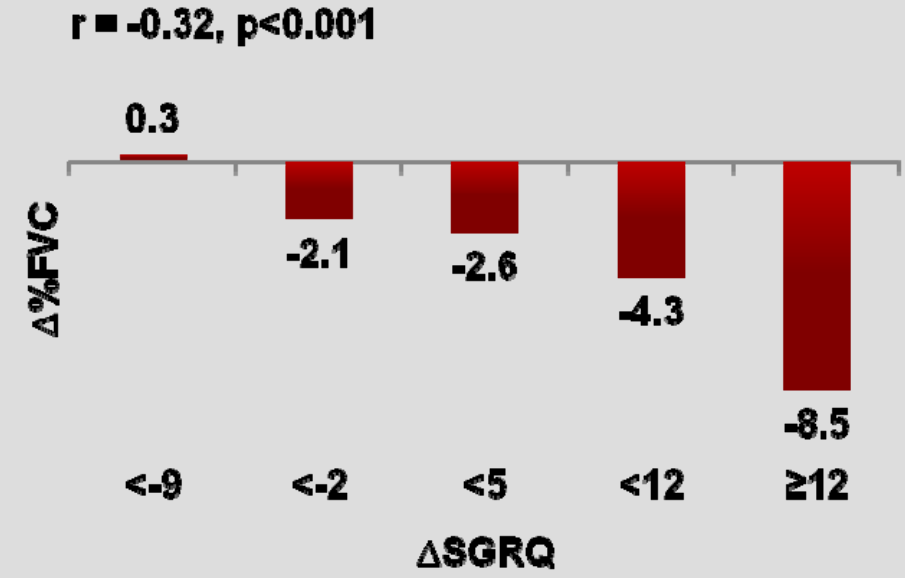
- Correlation coefficient (r) = 0.93, $p<0.001$
  - Mean interval between measurements, 18 days

Δ%FVC has Expected Graded Relationships with Changes in Other Measures

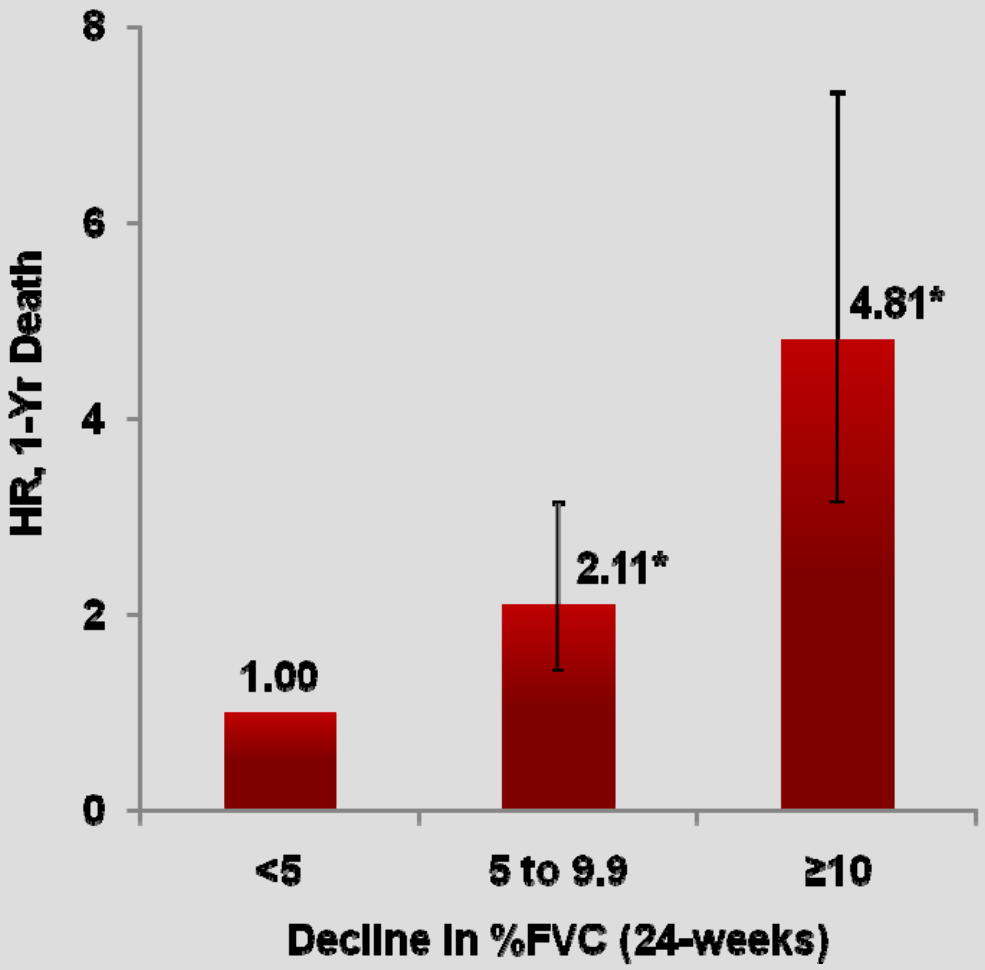


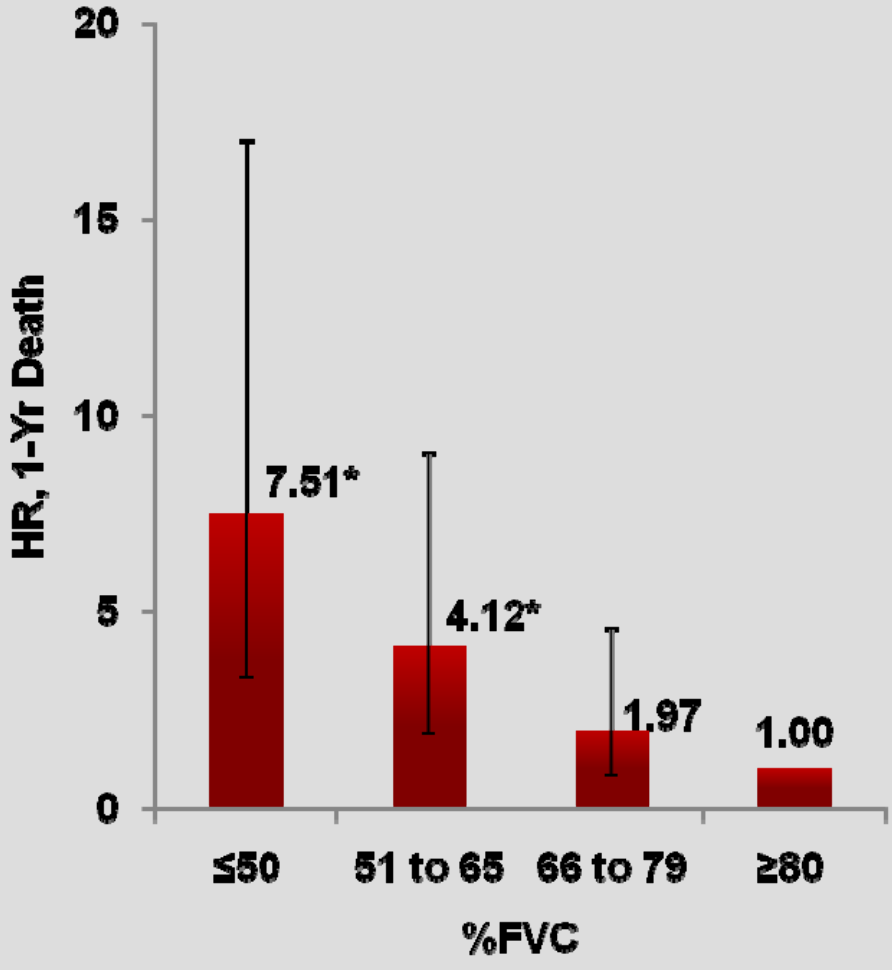






Δ%FVC is Predictive of Death at 1 Year

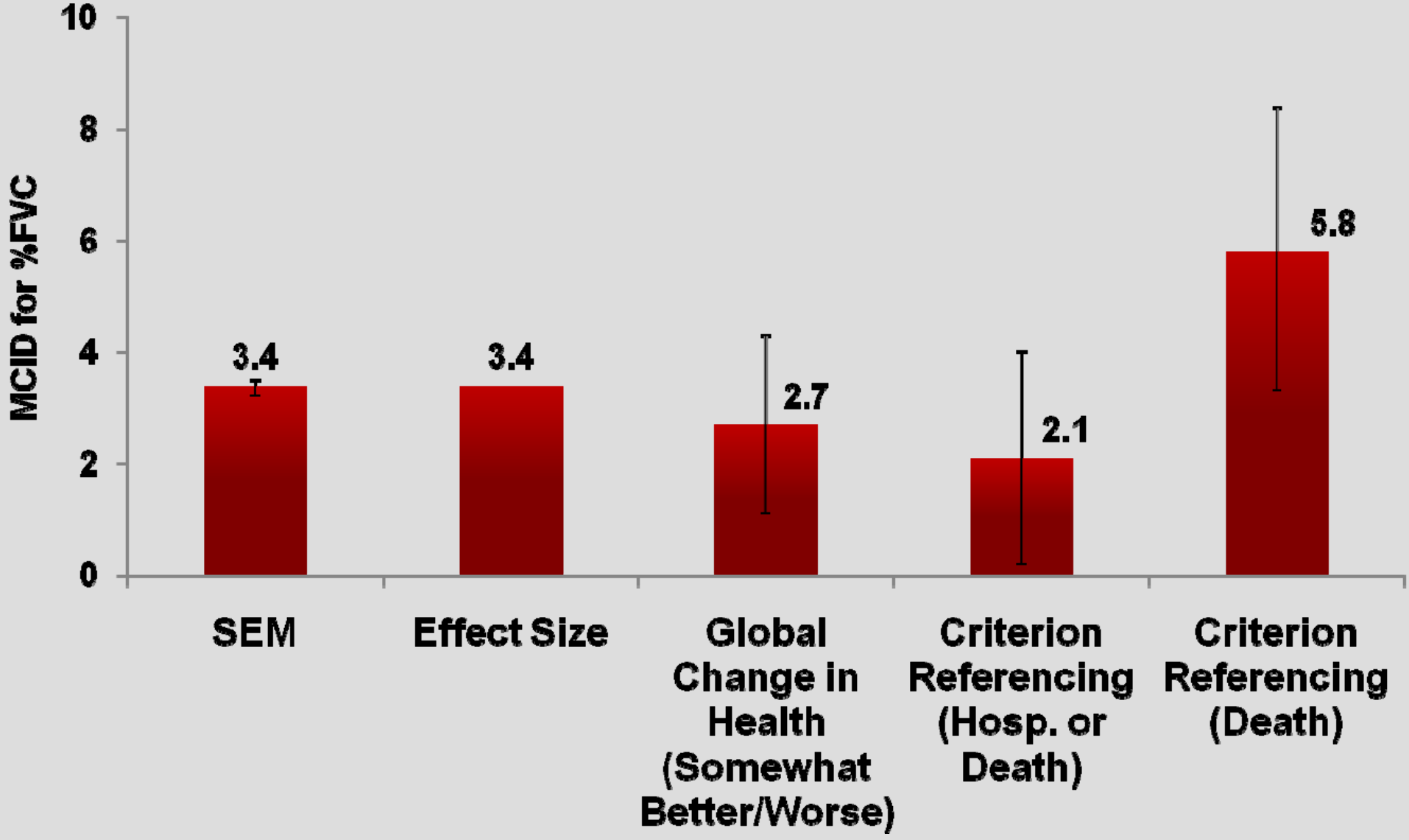




HR: hazard ratio

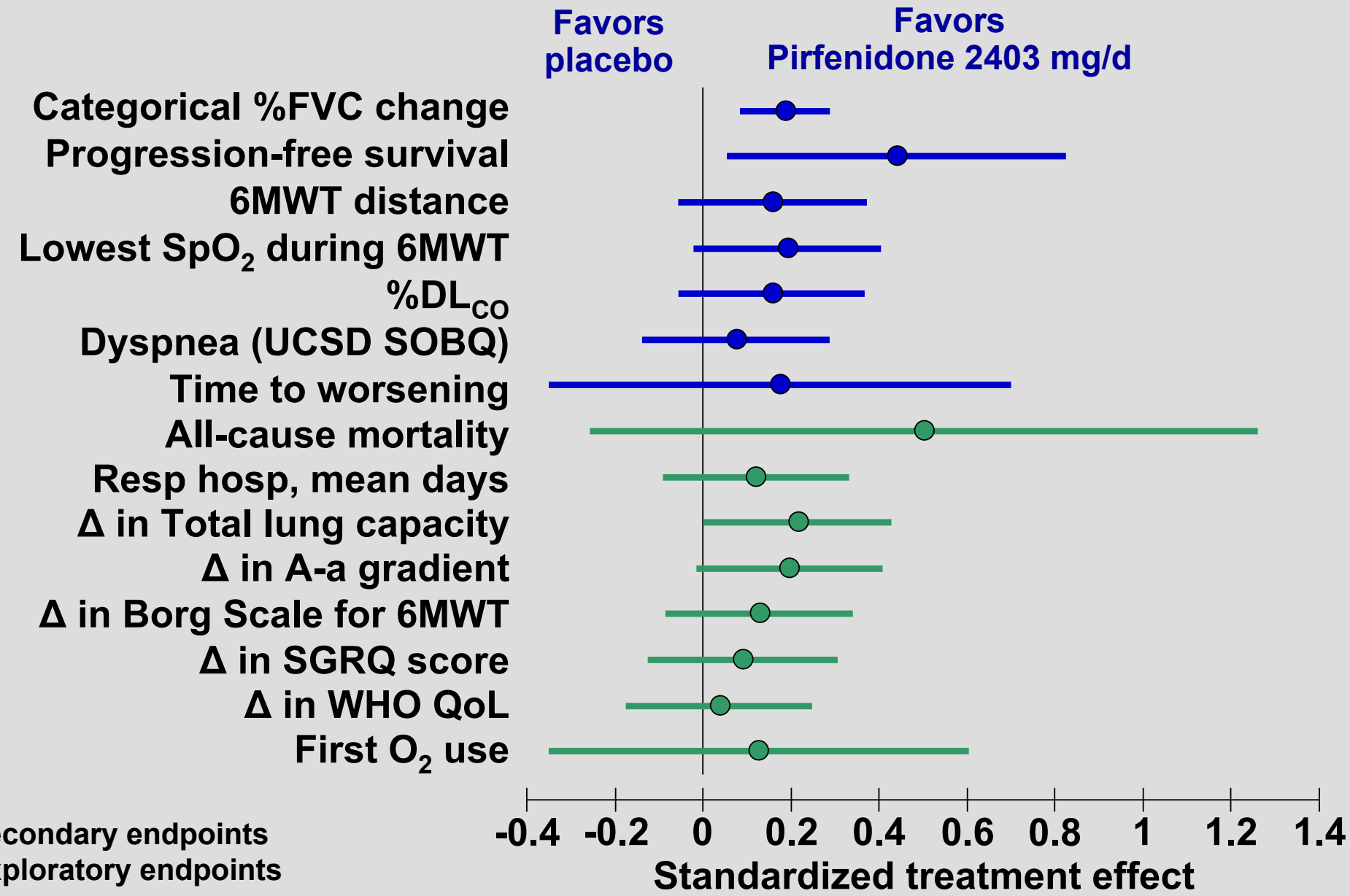
*p<0.001

3-Unit Change in %FVC is Clinically Significant

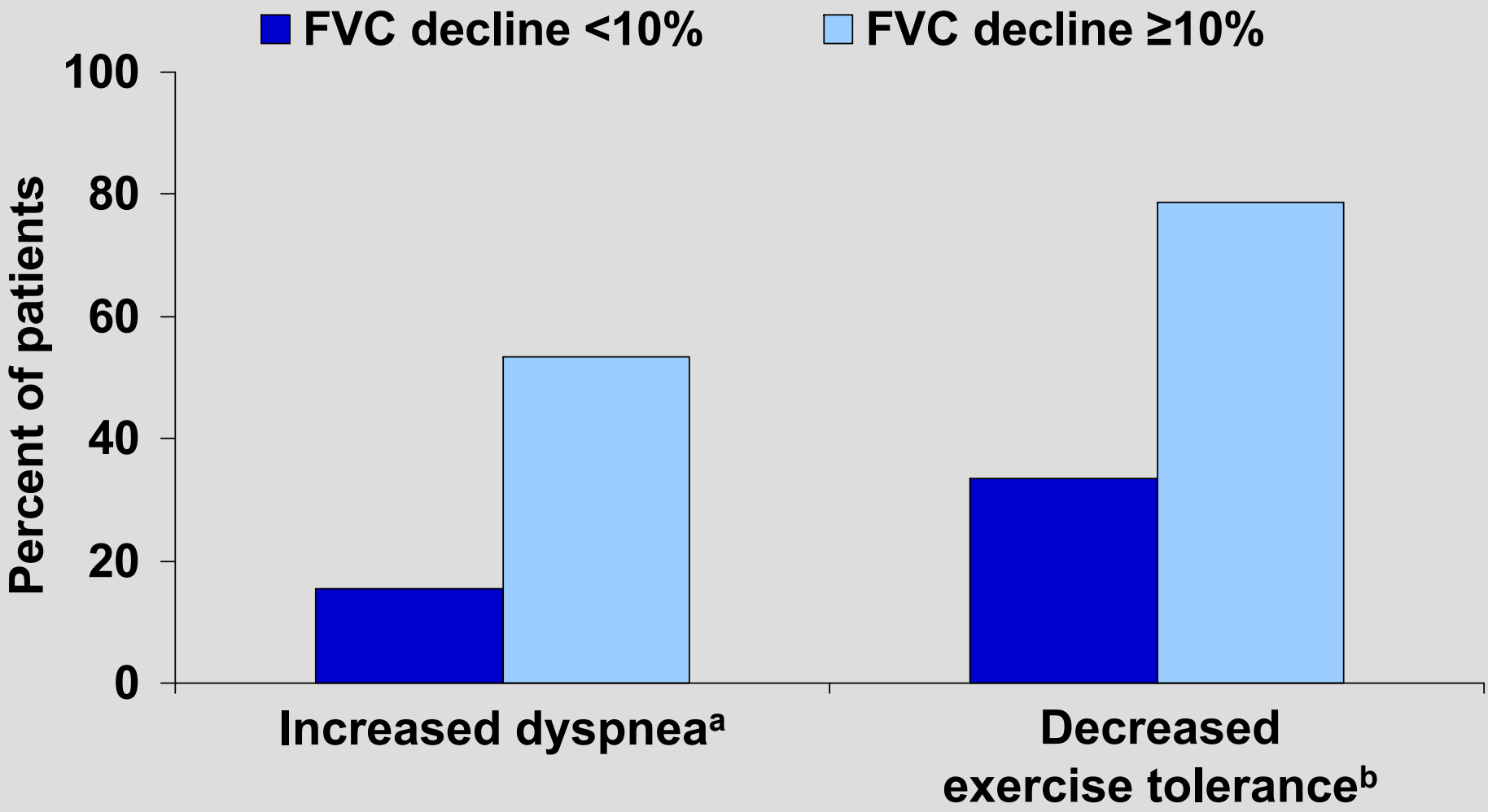


MCID: minimal clinically important difference

Secondary and Exploratory Endpoints
PIPF-004



Outcomes in Placebo Patients by FVC Decline



[a] Increased dyspnea: UCSD SOBQ increase ≥ 25.

[b] Decreased exercise tolerance: 6MWT distance decline ≥ 50m.

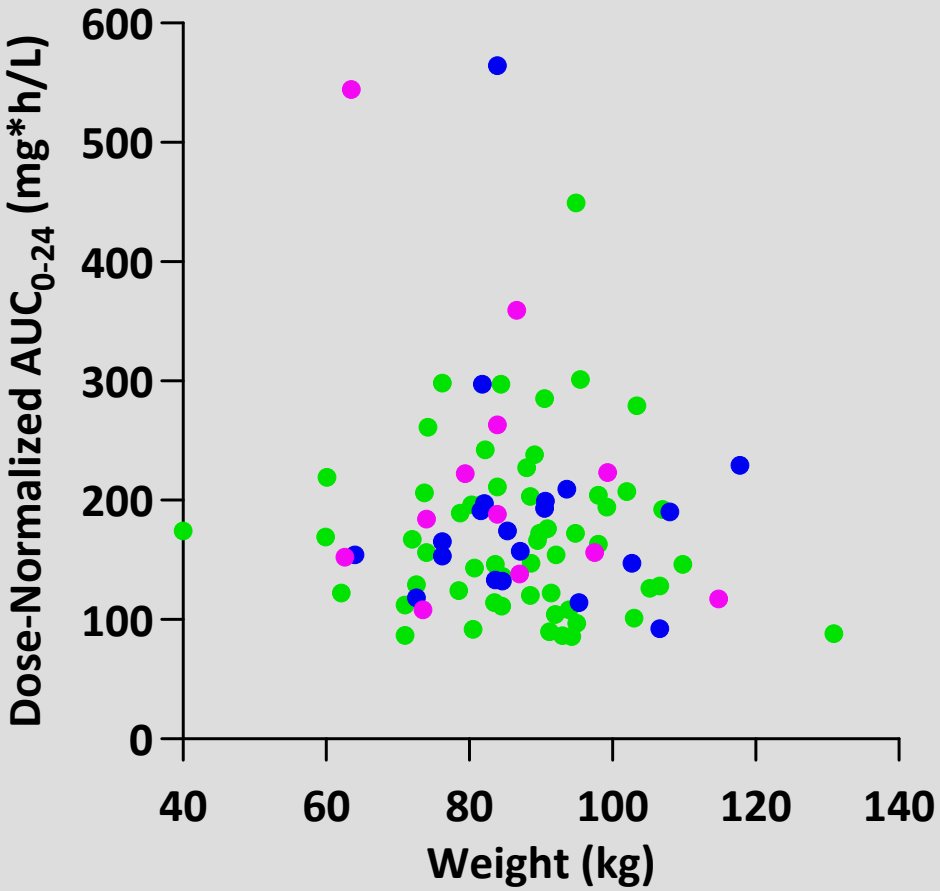
Primary, Secondary, and Survival Endpoints in PIPF-004 and PIPF-006

Outcome Variable	Study	Week 12	24	36	48	60	72
Percent Predicted FVC	PIPF-004	●	● ●	● ●	● ●	● ●	● ●
	PIPF-006	● ●	● ●	● ●	● ●	●	●
Categorical FVC	PIPF-004	●	● ●	● ●	● ●	● ●	● ●
	PIPF-006	●	● ●	● ●	●	●	●
6MWT Distance (m)	PIPF-004	●	●	●	●	●	●
	PIPF-006	●	● ●	● ●	● ●	● ●	● ●
Percent Predicted DL_{co}	PIPF-004	●	●	●	●	●	●
	PIPF-006	●	●	●	●	●	●
Worst SpO_2	PIPF-004	●	●	● ●	●	●	●
	PIPF-006	●	●	●	●	●	O
UCSD SOBQ	PIPF-004	O	●	●	●	●	●
	PIPF-006	O	●	O	●	●	●
Progression-Free Survival	PIPF-004	● ●					
	PIPF-006	●					
Worsening of IPF	PIPF-004	●					
	PIPF-006	●					
Survival	PIPF-004	●					
	PIPF-006	●					

- 74 of the 78 outcomes (94%) favored pirfenidone
- 23 (29%) outcomes had p-value < 0.05

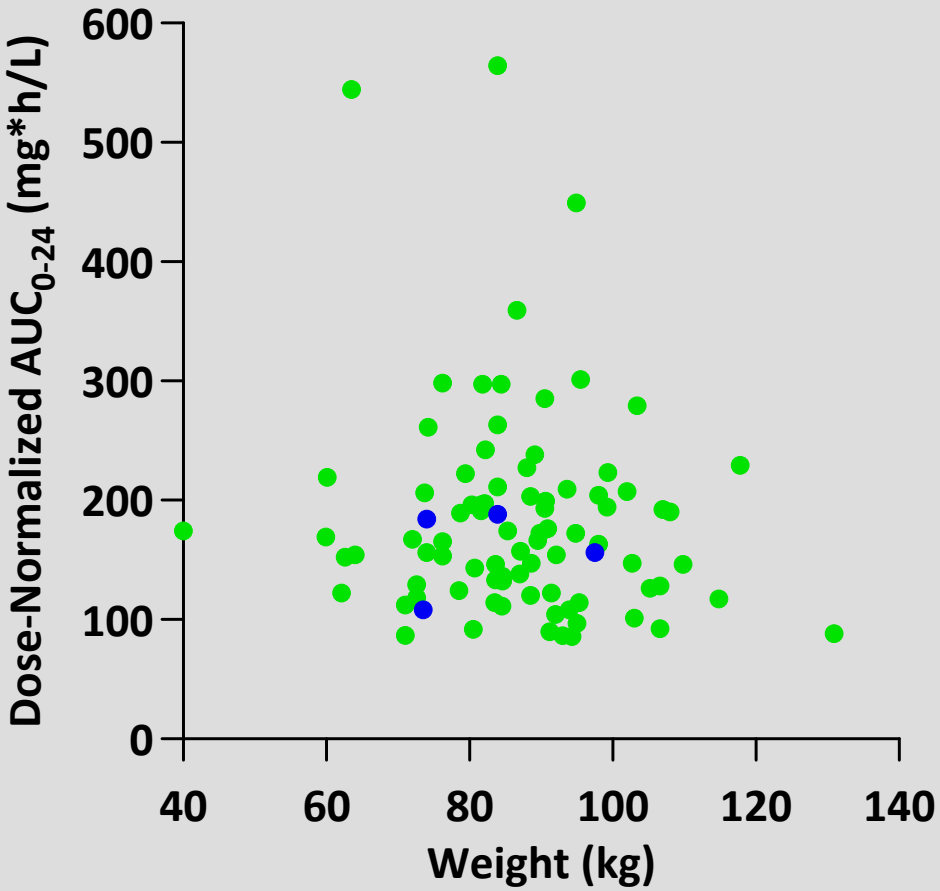
● ● Favors pirfenidone $p < 0.05$
● Favors pirfenidone $p > 0.05$
O Favors placebo

Population PK Screen
CYP1A2 Inhibitors



CYP1A2 Inhibitors, by Strength of Inhibition

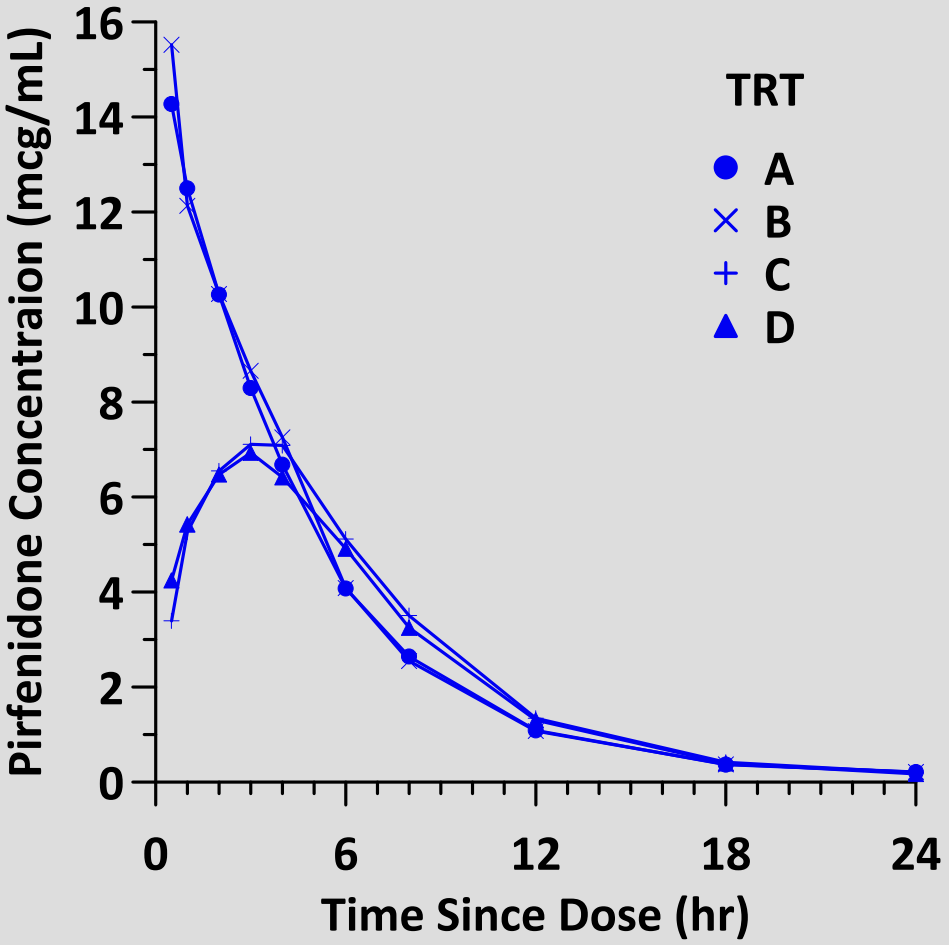
Green = None, Blue = Weak-Moderate, Pink = Strong



Ciprofloxacin Coadministration Only

Green = No, Blue = Yes

Food Effect and Adverse Events



- Differences between fed and fasted were under very strict conditions, real world factors will tend to moderate the differences
- AEs that were more likely in fasted state were relatively benign (nausea, headache, fatigue)

Rubino et al. Pulmonary Pharmacology and Therapeutics. 2009

Most Common TEAEs by SOC Leading to Dose Modification

System organ class preferred term	Patients, n (%)	
	Pirfenidone 2403 mg/d N = 345	Placebo N = 347
Patients with any TEAE leading to dose interruption or reduction	160 (46.4)	64 (18.4)
Skin and subcutaneous tissue disorders	69 (20.0)	9 (2.6)
Gastrointestinal disorders	65 (18.8)	22 (6.3)
Investigations	24 (7.0)	10 (2.9)
General disorders & admin site conditions	21 (6.1)	6 (1.7)
Nervous system disorders	16 (4.6)	6 (1.7)

Rate of Dose Modifications

	Pirfenidone 2403 mg/d N = 345	Placebo N = 347
Dose reduction, % pts	39	16
Median cumulative duration, days	70	5
Dose interruption, % pts	32	14
Median cumulative duration, days	15	15

Protocol Defined Dose Modifications

- Fatigue or gastrointestinal side effects
  - Dose modification as needed, restart as tolerated
  - Take with food
- Photosensitivity Rash
  - Mild to moderate photosensitivity rash
    - Dose modifications as needed, restart as tolerated
    - Sun avoidance precautions
  - Severe photosensitivity rash
    - Interrupt dosing, restart as tolerated
    - Sun avoidance precautions
- LFTs (ALT, AST)
  - Grade 1 or 2: dose modifications as needed, frequent monitoring
  - Grade 3 or higher: discontinue study drug

Adverse Events
Shionogi Post Marketing Surveillance*

Event, n	Non-serious	Serious
Decreased appetite	213	11
Abdominal discomfort	94	0
Nausea	85	3
Photosensitivity	74	2
Malaise	43	5
Somnolence	36	0
GGT increased	32	0
Dizziness	22	0
Diarrhea	20	2
Dysgeusia	20	0
Pneumonia	16	3
Pneumothorax	13	3

* ≥ 15 total events reported.