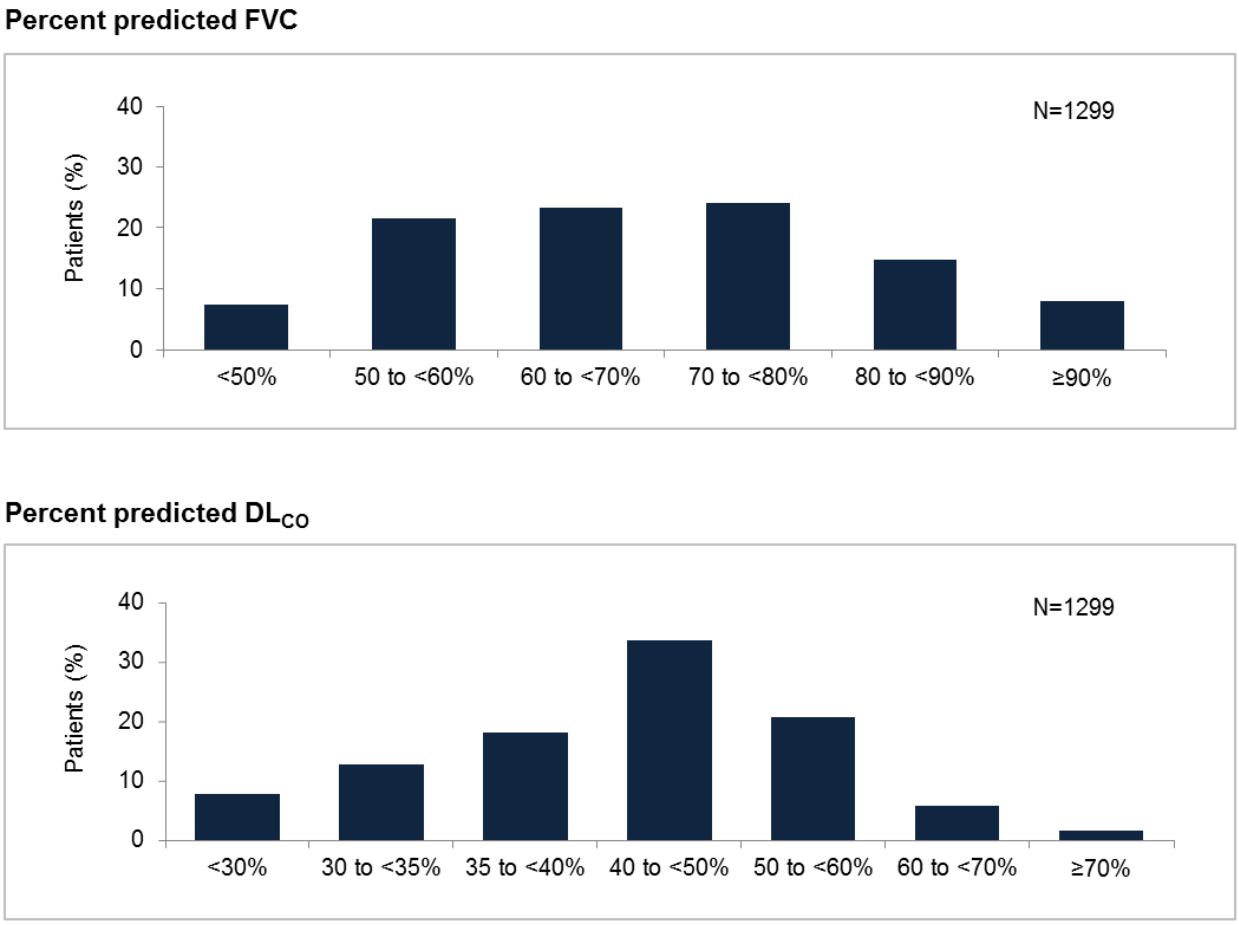
SUPPLEMENTAL MATERIAL

Table 1 Summary of eligibility criteria for the Phase 3 multinational studies

CAPACITY (Studies 004 and 006)	ASCEND (Study 016)
▪ Age 40 to 80 years ▪ Confident IPF diagnosis within the previous 48 months – Definite UIP on HRCT or probable UIP on HRCT + definite/probable UIP on surgical lung biopsy ▪ No evidence of improvement in disease severity within the preceding 12 months ▪ Percent predicted FVC ≥50% ▪ Percent predicted DL_{CO} ≥35% ▪ Either percent predicted FVC or percent predicted DL_{CO} ≤90% ▪ FEV1/FVC ratio ≥0.70 ▪ 6-minute walk distance ≥150 m	▪ Age 40 to 80 years ▪ Centrally confirmed IPF diagnosis according to 2011 ATS/ERS/JRS/ALAT criteria at least 6 months and not more than 48 months prior to randomization ▪ Clinical symptoms consistent with IPF of ≥12 months duration ▪ No evidence of improvement in disease severity within the preceding 12 months ▪ Percent predicted FVC ≥50% and ≤90% ▪ Percent predicted DL_{CO} ≥30% and ≤90% ▪ FEV1/FVC ratio ≥0.80 ▪ 6-minute walk distance ≥150 m

DL_{CO}=carbon monoxide diffusing capacity; FEV1=forced expiratory volume in 1 second; FVC= forced vital capacity; HRCT=high resolution computed tomography; IPF=idiopathic pulmonary fibrosis; UIP=usual interstitial pneumonia

Figure 1 Distribution of baseline values for percent predicted FVC and percent predicted DL_{CO} in the integrated population



DL_{CO}=carbon monoxide diffusing capacity; FVC=forced vital capacity

Table 2. Summary of treatment emergent adverse events

	Integrated Population (N=1299)*	Phase 3 Multinational Trials†	
		Pirfenidone (N=623)	Placebo (N=624)
Duration of exposure, median (range), yr	1.7 (>0, 9.9)	1.0 (>0, 2.3)	1.0 (>0, 2.3)
Any TEAE, %	97.6	99.0	97.9

Any serious TEAE, %	49.2	27.0	28.5
Any TEAE leading to treatment discontinuation, %	38.1	14.6	9.6

TEAE=treatment emergent adverse event

*Includes 2 patients in Study 002 with a diagnosis of “pulmonary fibrosis”

†CAPACITY (studies 004 and 006) and ASCEND (study 016)

Table 3. Most common treatment emergent serious adverse events*

Patients, %	Integrated Population (N=1299)†	Phase 3 Multinational Trials‡	
		Pirfenidone (N=623)	Placebo (N=624)
Any TE SAE	49.2	27.0	28.5
Idiopathic pulmonary fibrosis	17.5	5.3	9.3
Pneumonia	7.9	3.5	4.3
Respiratory failure	3.2	1.1	1.4
Atrial fibrillation	2.8	0.6	0.6
Bronchitis	2.7	0.5	1.4

TE SAE=treatment emergent serious adverse event

*Occurring in >2% of patients in the integrated population
†Includes 2 patients in Study 002 with a diagnosis of “pulmonary fibrosis”
‡CAPACITY (studies 004 and 006) and ASCEND (study 016)

Table 4. Liver-related outcomes

	Integrated Population (N=1299)†	**Phase 3 Multinational Trials‡**	
		Pirfenidone (N=623)	**Placebo (N=624)**
Duration of exposure, median (range), yr	1.7 (>0, 9.9)	1.0 (>0, 2.3)	1.0 (>0, 2.3)
ALT or AST Increased, %			
3 to 4.99 x ULN	1.9	2.4	0.5
5 to 9.99 x ULN	0.9	1.0	0.2
10 to 19.99 x ULN	0.2	0.3	0

≥20 x ULN	0	0	0.2
Serum total bilirubin >2 x ULN, %	0.3	0.2	0
Study treatment discontinuation, %*	1.4	1.0	0.3
Liver-related TE SAE, %*	1.0	1.0	0.2
Death, %*	0.2[§]	0	0

ALT=alanine aminotransferase; AST=aspartate aminotransferase; TE SAE=treatment emergent serious adverse event; ULN=upper limit of normal

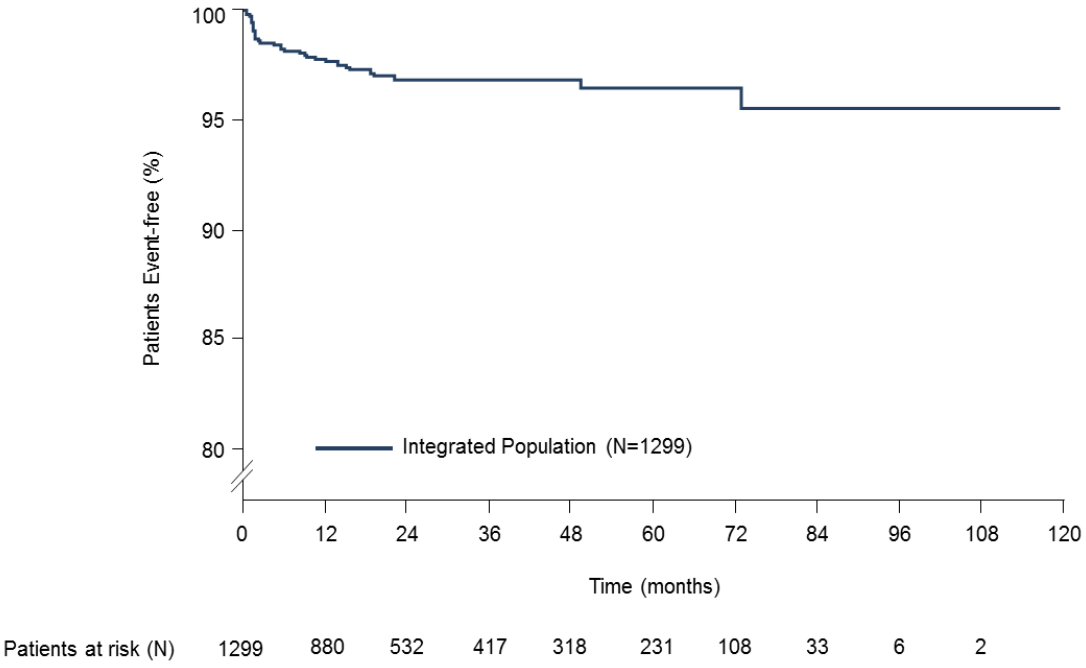
*Possibly due to any liver-related abnormality, including those without ALT or AST elevation

[†]Includes 2 patients in Study 002 with a diagnosis of “pulmonary fibrosis”

[‡]CAPACITY (studies 004 and 006) and ASCEND (study 016)

[§]One patient with hepatic hilus tumor and 1 patient with lung cancer and liver metastases

Figure 2 Kaplan-Meier estimate of time to onset of aminotransferase elevation ≥3 times the upper limit of normal



Patients at risk (N)	1299	880	532	417	318	231	108	33	6	2

Appendix 1 Exclusion criteria for the Phase 3 and open-label studies

A. CAPACITY (Studies 004 and 006)

Disease-related Exclusions

1. Not a suitable candidate for enrollment or unlikely to comply with the requirements of this study, in the opinion of the investigator
2. Premature withdrawal from a randomized IPF clinical trial in the previous 2 years for any reason other than Sponsor decision or current participation in a clinical drug trial
3. Forced expiratory volume in the first second (FEV1)/FVC ratio <0.7 after administration of bronchodilator at the Screen Visit and Day 1 before randomization
4. Bronchodilator Response defined by an absolute increase of ≥ 12% and an increase of 200 mL in the predicted FEV1 or FVC or both after bronchodilator Day 1 before randomization
5. Residual volume (RV) >120% of predicted (before administration of bronchodilator)
6. History of clinically significant environmental exposure known to cause PF (including but not limited to drugs, asbestos, beryllium, radiation, domestic birds)
7. Known explanation for interstitial lung disease, including but not limited to radiation, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV), viral hepatitis and cancer
8. Diagnosis of any connective tissue disease, including but not limited to scleroderma, systemic lupus erythematosus, and rheumatoid arthritis
9. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis
10. In the clinical opinion of the investigator, the patient is expected to need and be eligible for a lung transplant within 72 weeks after randomization
11. Unable to undergo pulmonary function testing, which includes meeting the following reproducibility standards:

    - At Screening, the 2 highest acceptable FVC values must be within 0.100 liter
    - At Day 1, the 2 highest acceptable FVC values must be within 0.100 liter
    - At Screening, 2 of the 3 acceptable DLco values must be within 2 units (for TL_{CO}, within 0.67 SI units) of each other

Medical Exclusions

12. Any history of malignancy likely to result in death or significant disability or likely to require significant medical or surgical intervention within the next 2 years. This does not include minor surgical procedures for localized carcinoma (e.g., basal cell carcinoma)
13. Any condition other than IPF which, in the opinion of the investigator, is likely to result in the death of the patient within the next 2 years
14. History of advanced cirrhosis or clinically significant liver disease
15. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous 6 months, including but not limited to the following:

    - Myocardial infarction, unstable angina pectoris, coronary artery bypass surgery, or coronary angioplasty
    - Congestive heart failure requiring hospitalization

- Uncontrolled arrhythmias
- Asthma or chronic bronchitis requiring hospitalization in the last 6 months

16. Any condition, which, in the opinion of the investigator, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone
17. Poorly controlled diabetes (defined by glycosylated hemoglobin [HbA1C] >10)
18. Pregnancy or lactation. Women of childbearing capacity are required to have a negative serum pregnancy test before treatment and must agree to maintain highly effective methods of contraception by practicing abstinence or by using at least two methods of birth control from the date of consent through the end of the study. If abstinence is not practiced, then one of the two methods of birth control should be an oral contraceptive (e.g., oral contraception and a spermicide).
19. History of alcohol or substance abuse in the past 2 years
20. History of any condition or habit associated with altered consciousness and a risk of aspiration in the past 2 years
21. Family or personal history of long QT Syndrome

Laboratory Exclusions

22. Any of the following liver function test criteria above specified limits: total bilirubin >2.5 × upper limit of normal (ULN); aspartate or alanine aminotransferase (AST/SGOT or ALT/SGPT) >2.5 × ULN; alkaline phosphatase >2.5 × ULN
23. Screening or Day 1 ECG with a QTcB interval >500 msec

Concomitant Therapy Exclusions

24. Prior use of pirfenidone or known hypersensitivity to any of the components of study treatment
25. Patients are excluded if they require the following therapies within 28 days prior to screening:

    a. Investigational therapy defined as any drug that has not been approved for marketing for any indication in the country of the participating site
    b. Any cytotoxic, immunosuppressive, cytokine modulating, or endothelin receptor antagonist agents including but not limited to: azathioprine, bosentan, cyclophosphamide, corticosteroids, cyclosporine, etanercept, iloprost, infliximab, leukotrienes, methotrexate, mycophenolate mofetil, sildenafil (daily), tetrathiomolybdate, TNF α inhibitors, N-acetyl-cysteine (NAC), imatinib mesylate, Interferon gamma-1b (IFN-γ 1b), and tyrosine kinase inhibitors
    c. Concomitant medications being used for the treatment of IPF (including but not limited to): ACE-inhibitors, colchicine, warfarin, heparin, sildenafil, and HMG-CoA reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication.

B. ASCEND (Study 016)

Disease-related Exclusions

1. Significant clinical worsening of IPF between Screening and Day 1, in the opinion of the investigator
2. Not a suitable candidate for enrollment or unlikely to comply with the requirements of this study, in the opinion of the investigator
3. Forced expiratory volume in one second (FEV1)/FVC ratio <0.8 after administration of bronchodilator at Screening, confirmed by central review
4. Bronchodilator response, defined by an absolute increase of ≥12% and an increase of 200 mL in the predicted FEV1 or FVC or both after bronchodilator use compared with the values seen before bronchodilator use at Screening, confirmed by central review
5. Cigarette smoking within 3 months of Screening or unwilling to avoid tobacco products throughout the study
6. History of clinically significant environmental exposure known to cause PF, including but not limited to drugs (such as amiodarone), asbestos, beryllium, radiation, and domestic birds
7. Known explanation for interstitial lung disease, including but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV), viral hepatitis, and cancer
8. Clinical diagnosis of any connective tissue disease, including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis
9. History of asthma or chronic obstructive pulmonary disease
10. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis
11. Expected to receive a lung transplant within 1 year from randomization or, for patients at sites in the United States (US), on a lung transplant waiting list at randomization

Medical Exclusions

12. Unable to perform 6MWT or to undergo pulmonary function test (PFT)
13. Any history of malignancy likely to result in significant disability or likely to require significant medical or surgical intervention within the next 2 years. This does not include minor surgical procedures for localized cancer (e.g., basal cell carcinoma)
14. Any condition other than IPF that, in the opinion of the investigator, is likely to result in the death of the patient within the next 2 years
15. History of severe hepatic impairment or end-stage liver disease
16. History of end-stage renal disease requiring dialysis
17. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous 6 months, including but not limited to the following:

    a. Unstable angina pectoris or myocardial infarction
    b. Congestive heart failure requiring hospitalization
    c. Uncontrolled clinically significant arrhythmias

18. Any condition that, in the opinion of the investigator, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone

19. Pregnancy or lactation. Women of childbearing capacity are required to have a negative serum pregnancy test before treatment and must agree to maintain highly effective contraception by practicing abstinence or by using at least two methods of birth control from the date of consent through the end of the study. If abstinence is not practiced, one of the two methods of birth control should be an oral contraceptive (e.g., oral contraceptive and a spermicide).
20. History of alcohol or substance abuse in the past 2 years
21. Family or personal history of long QT Syndrome

Laboratory Exclusions

22. Any of the following liver function test criteria above specified limits: total bilirubin above the upper limit of normal (ULN), excluding patients with Gilbert's syndrome; aspartate or alanine aminotransferase (AST/SGOT or ALT/SGPT) >3 × ULN; alkaline phosphatase >2.5 × ULN
23. Creatinine clearance (CrCl <30) mL/min, calculated using the Cockcroft-Gault formula
24. Electrocardiogram (ECG) with a QTcB interval >500 msec at Screening

Medication Exclusions

25. Prior use of pirfenidone or known hypersensitivity to any of the components of study treatment
26. Use of any of the following therapies within 28 days before Screening:

    a. Investigational therapy, defined as any drug that has not been approved for marketing for any indication in the country of the participating site
    b. Any cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agent including but not limited to azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, TNF-α inhibitors, N-acetylcysteine (NAC), imatinib mesylate, Interferon gamma-1b (IFN γ 1b), and tyrosine kinase inhibitors
    c. Medications that are specifically used for the treatment of IPF including but not limited to angiotensin converting enzyme (ACE) inhibitors, colchicine, corticosteroids, heparin, warfarin, and HMG-CoA reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication
    d. Fluvoxamine
    e. Sildenafil (daily use). *Note*: intermittent use for erectile dysfunction is allowed

C. RECAP (Study 012)

Disease-related Exclusions

Any patient who meets any of the following criteria is not eligible to participate in the study:

1. Is pregnant or lactating. Women of childbearing capacity are required to have a negative serum pregnancy test before treatment and must agree to maintain highly effective methods of contraception by practicing abstinence or by using at least two methods of birth control from the date of consent through the end of the study. If abstinence is not practiced, then one of the

two methods of birth control should be an oral contraceptive (e.g., oral contraception and a spermicide).

2. Has known hypersensitivity to any of the components of the study drug
3. In the opinion of the PI, is not a suitable candidate for study participation. The PI should carefully consider the risks and benefits of treatment if the patient's medical status has declined significantly during participation in CAPACITY.
4. Participates in another interventional clinical trial between the end of participation in the CAPACITY studies and planned entry into PIPF-012
5. Receives the following therapies within 28 days of the first dose of pirfenidone in this study (Day 1):

    a. Investigational therapy defined as any drug that has not been approved for marketing for any indication in the country of the participating site
    b. Angiotensin-converting enzyme (ACE)-inhibitors, colchicine, warfarin, heparin, sildenafil, and hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication.
    c. Any cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agent including but not limited to: bosentan, cyclosporine, etanercept, iloprost, infliximab, leukotrienes, methotrexate, mycophenolate mofetil, sildenafil (daily), tetrathiomolybdate, TNF-α inhibitors, N-acetylcysteine (NAC) alone, imatinib mesylate, Interferon gamma-1b (IFN-γ 1b), and tyrosine kinase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication. *Note*: the exceptions are (a) corticosteroids, azathioprine, and/or cyclosphosphamide at doses specified in the ATS/ERS 2005 Guidelines and (b) NAC in combination with prednisone and azathioprine.

6. Permanently discontinues study drug in the CAPACITY studies for any reason
7. Meets any of the following liver function test criteria above specified limits at the CAPACITY Treatment Completion Visit: total bilirubin >2.5 × upper limit of normal (ULN); aspartate or alanine aminotransferases (AST/SGOT or ALT/SGPT) >2.5 × ULN; alkaline phosphatase >2.5 × ULN
8. Has and ECG from a CAPACITY Trials Treatment Completion Visit or from the PIPF-012 Day 1 Visits showing heart-rate–correct (using Bazett's formula) QT (QTcB) interval >500 ms or must obtain permission from the InterMune medical monitor

D. Study 002

Exclusion Criteria

Patients with any of the following will be excluded from the study:

1. Patient not a suitable candidate for study participation for any reason in opinion of Investigator or Sponsor
2. Pregnant or breast feeding
3. Concomitant administration of any of the following: Interferon gamma 1-β or other interferons, colchicine, allopurinol, azathioprine, cyclophosphamide, other cytotoxic agents, cyclosporine, D-penicillamine, methotrexate, bosentan, etanercept, infliximab, or N-acetylcysteine