Methods 109 EU sites dosed 1006 patients. Safety data were recorded at routine clinic visits for up to 2 years. Pirfenidone-associated adverse drug reactions (ADR) were collected.

Results At baseline, mean±SD age was 70 ± 8.5 years and mean ±SD time since IPF diagnosis was 1.6 ± 2.5 years; 80% of patients were male; supplemental oxygen was used by 27% of patients; mean±SD FVC was 2.56 ± 0.78 L; mean±SD% predicted FVC was 66 ± 16% (14% had <50% predicted FVC). The most common comorbidities (>10%) were hypertension, gastroesophageal reflux disease, hypercholesterolemia and coronary artery disease.

At this interim analysis, median time on pirfenidone was 7.6 months and total exposure was 803 patient-years. Overall, 67% of patients had ≥1 ADR, most commonly: nausea, 17%; fatigue, 15%; decreased appetite, 13%; decreased weight, 12%; rash, 10%; and diarrhoea, 9%. Of patients who had an ADR, 55% experienced their first ADR within the first 30 days' treatment. Around 5% of patients completed 2 years' treatment, 55% are ongoing, 9% died and 21% discontinued due to pirfenidone-related ADRs (most commonly nausea, rash and decreased weight). 11% discontinued for other reasons.

Patients with FVC <50% had a higher discontinuation rate than other patients (48% vs 39%, respectively). The imbalance was mainly driven by higher rates of death and lung transplantation. The discontinuation rate due to pirfenidone ADRs was similar among patients with FVC <50% and ≥50% (20.3% vs 20.9%, respectively).

62% of patients received pirfenidone alone; 11%, 8% and 8% received pirfenidone plus NAC, CS, or NAC+CS, respectively. The remaining 11% had partial use of NAC and/or steroids. ADR incidence was generally consistent for these subgroups except weight decrease and ALT increase, which occurred more often in the pirfenidone+CS group.

Conclusions In this real-world setting, pirfenidone was generally safe and well tolerated as monotherapy or combined with NAC and/or CS. The rate of discontinuation due to pirfenidone-related ADRs was similar regardless of disease severity.

P13 SAFETY OF PIRFENIDONE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF): INTEGRATED ANALYSIS OF CUMULATIVE DATA FROM 5 CLINICAL TRIALS

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Introduction and objectives IPF is a chronic, progressive and irreversible disease that requires long-term clinical management. To further evaluate the clinical safety of pirfenidone in patients with IPF, we performed a comprehensive integrated analysis of safety data from 5 clinical trials.

Methods All patients assigned to receive pirfenidone (2403 mg/d) in the Phase 3 ASCEND (016) and CAPACITY (004/006) studies and all patients receiving ≥1 dose of pirfenidone in either of two ongoing open-label studies (studies 002 and 012) comprised the integrated population. EAP (002) is a compassionate use study in the U.S.; RECAP (012) is evaluating pirfenidone in patients who completed one of the Phase 3 studies. Analyses were based on the January 15, 2014 interim data cut.

Results 1299 patients were included in the integrated population. The cumulative total exposure to pirfenidone was 3160 person exposure years (PEY). The median duration of exposure was 1.7 years (range, 1 week–9.9 years); 545 (42%) patients received pirfenidone for ≥2 years and 325 (25%) patients received pirfenidone for ≥4 years. The majority of patients (75.8%) received a mean daily dose of ≥1800 mg. Consistent with prior observations, gastrointestinal and skin-related events were among the most common treatment emergent adverse events (Table 1); these were almost always mild to moderate in severity, reversible with dose modification and rarely led to treatment discontinuation. Cough, dyspnoea and IPF were the most common respiratory adverse events in the integrated population—a finding that is consistent with expectations in patients with a chronic progressive respiratory disease followed over a long period of observation. Aminotransferase (ALT or AST) elevations (>3 × ULN) occurred in 40/1299 (3.0%) patients in the integrated population.

Abstract P13 Table 1 Treatment emergent adverse events in the integrated population compared with the pooled pirfenidone 2403 mg/d and placebo groups in the Phase 3 trials*

	Integrated population (N = 1299)† OE = treatment emergent adverse event ment emergent adverse events d sun exposure during treatment with pirfenidone. the skin du
Median (range) duration of exposure, yr	1.7 (>0, 9.9)
Treatment emergent adverse event,%	
Nausea	37.6
Cough	35.1
Dyspnea	30.9
Upper respiratory tract infection	30.6
Idiopathic pulmonary fibrosis	29.3
Fatigue	28.2
Diarrhoea	28.1
Rash	25.0
Bronchitis	23.8
Headache	21.6
Nasopharyngitis	21.3
Dizziness	21.2
Dyspepsia	18.4
Vomiting	15.9
Weight decreased	15.6
Back pain	15.4
Anorexia	15.2

*Occurring in ≥15% of patients in the cumulative clinical database.
†Includes 2 patients in Study 002 with a diagnosis of "pulmonary fibrosis."

Conclusions A comprehensive integrated analysis of safety outcomes in a large, well–defined cohort of 1299 patients with IPF who were treated with pirfenidone for up to 9.9 years demonstrated that treatment with pirfenidone is safe and generally well tolerated. These observations provide further evidence to support the long-term clinical safety of pirfenidone in patients with IPF.

P14 PIRFENIDONE IS EFFICACIOUS IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF) WITH MORE PRESERVED LUNG FUNCTION

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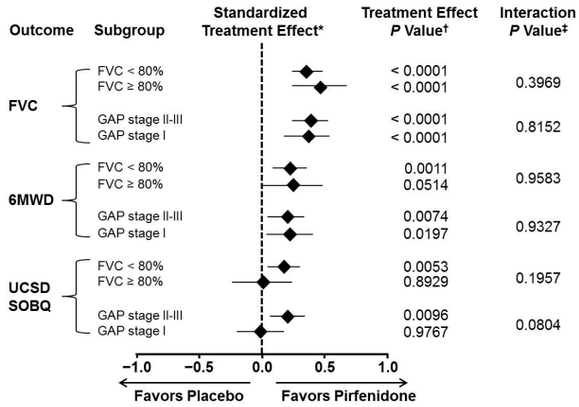
Introduction and objectives IPF is a progressive, irreversible and fatal disease. Early treatment initiation when lung function is relatively preserved may have beneficial outcomes; however, published data to support this hypothesis are lacking. We investigated the efficacy of pirfenidone at 12 months in patients stratified by lung function using forced vital capacity (FVC) or GAP stage.

Methods Efficacy outcomes (FVC, 6-minute walk distance [6MWD] and dyspnea [UCSD SOBQ]) were analysed at 12 months in patients randomised to pirfenidone 2403 mg/d or placebo in the pooled CAPACITY/ASCEND population (N = 1247), stratified by baseline FVC (≥80%, <80%) and GAP stage (GAP I, GAP II-III). Treatment-by-subgroup interaction was tested based on a rank ANCOVA model. The factors in the model included study, region, treatment, subgroup and treatment-by-subgroup interaction term.

Results Demographic characteristics were similar across all four groups. In the placebo arm, disease progression as measured by FVC occurred with comparable frequency in patients with FVC ≥80% and FVC <80%, as well as in patients with GAP I and GAP II-III stage. A higher proportion of placebo patients with FVC <80% and GAP II-III stage had a ≥50-m decline in 6MWD or death or a ≥20-point change in the UCSD SOBQ total score. Pirfenidone treatment reduced the proportion of patients experiencing a ≥10% FVC decline or death and increased the proportion of patients with no FVC decline in all subgroups. Pirfenidone also reduced the proportion of patients with ≥50-m decline in the 6MWD or death and increased the proportion of patients with no 6MWD decline in all subgroups. The magnitude of treatment effect in patients with less *vs* more preserved lung function was comparable, with no significant treatment-by subgroup interaction (Figure 1).



6MWD, 6-minute walk distance; FVC, forced vital capacity; UCSD SOBQ, University of California—San Diego Shortness of Breath Questionnaire.
*For FVC and 6MWD: treatment difference = pirfenidone – placebo; for UCSD SOBQ, treatment difference = placebo – pirfenidone.
†*P* values represent categorical difference (pirfenidone *versus* placebo). Percentage relative treatment difference in the proportion of patients achieving efficacy outcomes were calculated using the following formula: 100 × [pirfenidone – placebo]/[placebo].
‡The *P* value is from the test statistic for testing the interaction between the treatment and subgroup variable.

Abstract P14 Figure 1 Treatment effect of pirfenidone by baseline lung function

Conclusions In the placebo population, clinically significant disease progression occurs in subgroups with more and less preserved lung function at baseline, underlying the need for early intervention. The magnitude of pirfenidone treatment effect on functional measures was comparable in these subgroups of patients (FVC <80% *vs* FVC ≥80% or GAP I vs GAP II-III stage), supporting the initiation of treatment soon after diagnosis, when pulmonary function is relatively preserved.

Clinical studies of advanced COPD

P15 REGIONAL CEREBRAL ATROPHY AND COGNITIVE FUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background Widespread white matter damage and cognitive impairment have been demonstrated in COPD. However, it remains unclear if regional atrophy is present. We used a simple clinical visual rating scale to measure regional atrophy in a well-characterised population with COPD and compared age-matched controls. We explored correlations with demographics, disease factors and cognitive measures.

Objectives

1. a) To determine if there are significant differences in regional atrophy between COPD patients and age-matched control subjects.
2. b) To investigate whether patient characteristics or measures of disease severity account for group differences in atrophy severity.
3. c) To seek correlations with regional atrophy.

Methods A validated visual analogue MRI grading technique was used to assess the degree of atrophy in multiple brain regions in stable non-hypoxaemic COPD patients (n = 25) and age-