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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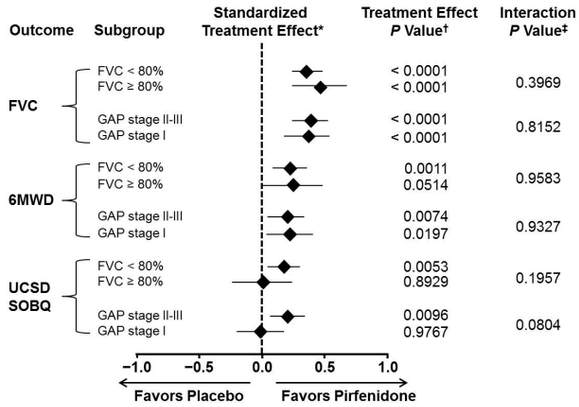
Introduction and objectives IPF is a progressive, irreversible and fatal disease. Early treatment initiation when lung function is relatively preserved may have beneficial outcomes; however, published data to support this hypothesis are lacking. We investigated the efficacy of pirfenidone at 12 months 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-

matched control subjects (n = 25). This study is a further analysis of a previous case-control multi modal cranial MRI study.[1]

Main results COPD patients had significantly greater frontal atrophy than control subjects (p = 0.01), this was independent of smoking history, comorbidities and hospital anxiety and depression scores. Cognitive function was significantly worse in the COPD group for executive function, working memory, verbal memory and processing speed. Group differences in atrophy did not seem to account for differences in cognitive function. We were unable to identify meaningful correlations between regional atrophy and disease severity or cognitive function.

Abstract P15 Table 1 Bilaterally summed composite scores for regional atrophy in the control and COPD group (presented as Mean ± SD)

	Control subjects (n=25)	COPD patients (n=25)	P value	Corrected p value**
Frontal	5.08 ± 2.68	7.32 ± 3.26	0.01*	0.02*
Temporal	5.76 ± 3.27	7.72 ± 4.77	0.10	0.06
Hippocampal	4.60 ± 1.89	5.24 ± 3.06	0.38	0.05
Parahippocampal	1.68 ± 1.97	3.72 ± 2.75	0.13	0.005

***Generalised linear model multivariate analysis controlling for group differences in Charlson, pack years and HAD scores.*
**Statistically significant result*

Conclusions There is significant frontal brain atrophy in stable non-hypoxaemic COPD patients. This regional atrophy does not appear to be related to disease severity or cognitive function. Further work is needed to identify causative mechanisms behind this structural change.

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P16 PROSPECTIVE RISK OF OSTEOPOROTIC FRACTURE IN PATIENTS WITH ADVANCED COPD

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Introduction COPD is associated with an increased prevalence of osteoporosis with shared risk factors including smoking, low BMI and reduced mobility. However, the risk of future fractures is not routinely considered in the management of COPD. We aimed to quantify future fracture likelihood and identify factors associated with an increased probability of osteoporotic fractures in patients with advanced COPD.

Methods Patients with advanced COPD were prospectively recruited and underwent a 'comprehensive respiratory assessment' as previously described.[1] The 10 year probability of developing either a major osteoporotic fracture or hip fracture was calculated using the fracture risk assessment tool (FRAX®)[2] using routinely collected data including age, gender, weight, height, smoking history, alcohol use, presence of inflammatory arthritis, corticosteroid use, but with the omission of family history and prior history of fractures. High risk was considered to be a ≥20% probability of a major osteoporotic fracture and ≥5% probability of a hip fracture.

Results 181 patients were included: mean (SD) age of 65 (9) years, MRC score 4 (IQR 0), BMI 25.4 (6.9) kg/m^2, 42% female and 25% current smokers. The mean (SD) 10-year probability for a major osteoporotic fracture was 9.1 (5.1)% and for a hip fracture was 3.5 (3.6)%. 43 (24)% of patients were considered to be high probability of a future fracture.

25 (14%) patients were prescribed a bisphosphonate and 17 (9%) maintenance daily oral prednisolone. Only 4 (24%) patients on oral steroids had a high probability for a future osteoporotic fracture.

The cohort was divided into quartiles based on FRAX® score for future major osteoporotic fractures. There were significant differences between groups in exercise capacity, quadriceps strength, exacerbations, body composition and a trend to home oxygen use (Table 1).

Conclusion A quarter of patients with advanced COPD had a high probability of a future major osteoporotic fracture despite our calculations being an underestimate. An increased likelihood of fracture was associated with a number of potentially modifiable measures including exacerbation frequency, reduced physical performance and reduced skeletal muscle bulk.

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Abstract P16 Table 1 Characteristics of patients with advanced COPD divided into quartiles based on FRAX® 10 year major osteoporotic fracture risk

	Total (n = 181)	Quartile 1 (n = 45)	Quartile 2 (n = 44)	Quartile 3 (n = 44)	Quartile 4 (n = 48)	P value
FRAX major osteoporotic fracture (%)	9.1 (5.1)	4.3 (0.9)	6.6 (0.6)	8.9 (0.73)	16.0 (4.6)	
FRAX hip fracture (%)	3.5 (3.6)	0.7 (0.4)	1.7 (0.9)	3.3 (1.5)	7.8 (4.1)	<0.001
FEV_1 (L)	0.81 (0.44)	1.05 (0.68)	0.88 (0.32)	0.71 (0.25)	0.66 (0.41)	<0.001
Home oxygen (% yes)	39%	24%	39%	41%	52%	0.057
Exacerbations in previous year	4.7 (4.3)	2.8 (2.8)	5.5 (4.9)	4.8 (3.6)	5.5 (5.1)	0.007
Hospitalisations in previous year	1.3 (2.1)	1.1 (1.7)	1.4 (2.9)	1.3 (1.8)	1.4 (2.1)	0.753
CAT score	25.8 (6.9)	25.8 (7.7)	24.8 (6.8)	26.8 (6.4)	25.8 (6.7)	0.656
Incremental Shuttle Walk Test (m)	150 (110)	220 (160)	160 (80)	110 (60)	90 (40)	<0.001
Quadriceps Strength (Kg)	18.5 (7.3)	23.5 (8.6)	20.0 (6.5)	16.9 (4.6)	13.7 (5.0)	<0.001
Fat Free Mass Index (kg/m^2)	16.4 (2.6)	18.0 (2.8)	17.0 (1.9)	15.9 (2.6)	14.8 (2.0)	<0.001
Skeletal Muscle Index (kg/m^2)	6.1 (1.3)	6.7 (1.2)	6.6 (1.2)	5.8 (1.1)	5.4 (1.1)	<0.001
Total Bone Calcium (Kg)*	2.47 (0.62)	2.75 (0.53)	2.65 (0.48)	2.40 (0.52)	2.10 (0.73)	<0.001
Vitamin D (nmol/l)	29 (26)	30 (28)	29 (24)	34 (28)	22 (25)	0.220

Quartile 1 is the lowest risk and quartile 4 is the highest risk. Data are mean (SD). *calculated from DEXA.