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Early View

Research letter

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Effect of pirfenidone on breathlessness in patients with idiopathic pulmonary fibrosis

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Social media summary: New *post hoc* analysis of IPF clinical trials suggests that treatment with pirfenidone slows the worsening of patient-reported breathlessness over 12 months vs placebo in patients with more advanced disease (GAP Stage II/III or %FVC <80%).

To the Editor:

Dyspnoea is a frequent and debilitating symptom in patients with idiopathic pulmonary fibrosis (IPF) and is reported as the most important factor determining their health-related quality of life (QoL) [1-3]. Previous *post hoc* analysis of pooled data from IPF clinical trials has shown that a worsening of dyspnoea was particularly likely in patients with more severe versus less severe disease [4]. Interestingly, it has been suggested that patients with more severe disease may experience a greater benefit from pirfenidone on categorical worsening of dyspnoea or death compared with patients with less severe disease [4]. Here, we report the results of a *post hoc* analysis aiming to further examine the effect of pirfenidone compared with placebo on dyspnoea severity in patients with IPF, including the change from baseline in dyspnoea over 12 months and categorical changes in dyspnoea at 12 months.

This *post hoc* analysis included all patients randomised to treatment with pirfenidone 2403 $mg \cdot day^{-1}$ or placebo in the ASCEND (Study 016, NCT01366209) [5] and CAPACITY (Studies 004 and 006, NCT00287716 and NCT00287729) [6] Phase III clinical trials who completed the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ) at baseline. Patients were pooled and stratified by baseline Gender, Age, Physiology (GAP) Stage I versus Stage II/III and by baseline percent predicted forced vital capacity (FVC) ≥80% versus <80%. Patients completed the UCSD SOBQ at 12-week (CAPACITY) or 13-week (ASCEND) intervals and outcomes were assessed up to Week 52 [7]; higher scores indicated more breathlessness [1].

Changes in UCSD SOBQ score were compared using the Hodges-Lehmann estimate of the median differences between treatment groups in changes from baseline to Month 12 with 95% confidence intervals. Missing data were imputed using the sum of squared differences (SSD) method; deaths were assigned the highest UCSD SOBQ score of 120 points. Categorical changes in UCSD SOBQ score of <0, 0 to <10, 10 to <20, 20 to <30 and ≥30 points were also considered and compared using the Mantel-Haenszel chi-squared test. Percentages of patients with a change of ≥5, ≥10 or ≥20 UCSD

SOBQ points, or death, at Month 12 were summarised and compared using a chi-squared test. Missing data were imputed using the SSD method; deaths were added to the group with the highest categorical change in UCSD SOBQ.

In total, 1234 patients were included in this *post hoc* analysis (pirfenidone, n= 617; placebo, n=617). Baseline data for this population have been previously reported [4, 7]. In patients with GAP Stage II/III, those who received pirfenidone reported a significantly lower median change in UCSD SOBQ score from baseline to Month 12 compared with placebo (9.2 versus 13.0 points, respectively; p=0.009) (Figure 1a). A significantly lower median change in UCSD SOBQ score from baseline to Month 12 was also observed in patients with percent predicted FVC <80% who received pirfenidone compared with placebo (8.5 versus 12.0 points, respectively; p=0.006) (Figure 1b). There were no significant differences in changes observed from baseline to Month 12 in patients with GAP Stage I or percent predicted FVC ≥80% who received pirfenidone compared with placebo.

There was a significant difference between the pirfenidone and placebo groups for the categorical change in UCSD SOBQ score from baseline at 12 months in both the GAP Stage II/III (p=0.013; Figure 1c) and percent predicted FVC <80% (p=0.005; Figure 1d) groups. In both these groups, a greater percentage of patients treated with pirfenidone were in the <0, 0 to <10 and 10 to <20 categories of change in UCSD SOBQ score compared with placebo, while a greater percentage of placebo patients were in the 20 to <30 and ≥30 categories compared with pirfenidone (Figures 1c, d). In patients with GAP Stage I or percent predicted FVC ≥80%, no significant differences in categorical changes in UCSD SOBQ scores from baseline were observed at Month 12 in patients who received pirfenidone compared with placebo.

This *post hoc* analysis showed that pirfenidone reduced the worsening of patient-reported breathlessness in patients with percent predicted FVC <80% and/or those with GAP Stage II/III, and that this effect was evident over the full 12-month treatment period. These findings are important because dyspnoea is one of the most debilitating symptoms of IPF and negatively impacts patients'

QoL [1, 8]. Furthermore, based on a minimum clinically important difference of 8 points in UCSD SOBQ score estimated using data from patients with more advanced IPF in the STEP-IPF trial of sildenafil [1], the change in UCSD SOBQ scores seen in the placebo arm of our analyses for GAP Stage II/III or percent predicted FVC <80% represented a clinically significant deterioration.

The effect of pirfenidone on dyspnoea was only observed in patients with greater lung function impairment (percent predicted FVC <80%) or those with GAP Stage II/III. Dyspnoea was not specifically assessed in the INPULSIS trials of nintedanib, making direct comparisons challenging [9]; however, QoL was assessed across patient subgroups (percent predicted FVC ≤70% and >70%) using the St. George's Respiratory Questionnaire and similar findings were observed [10]. The absence of effect in the group of patients with less advanced disease is similar to the results presented in this subgroup analysis.

In daily clinical practice, there is sometimes hesitation to start antifibrotic treatment in patients with IPF who have less advanced disease or who are asymptomatic [11]. Although a treatment benefit on dyspnoea was not observed in patients with percent predicted FVC ≥80% or GAP Stage I, pirfenidone has been shown to have equally beneficial effects on disease progression endpoints, including FVC or death, in these subgroups [4]. Importantly, analysis of data from the open-label, long-term extension study of the ASCEND and CAPACITY trials (RECAP) showed that patients treated with placebo in CAPACITY experienced a reduction in the annual rate of lung function decline once pirfenidone was initiated. However, the lung function lost while they received placebo was not recovered once pirfenidone treatment was started [12]. The available data underline the unmet need to begin treatment in a timely manner and reduce the rate of further lung function decline [4, 13].

There are a number of limitations to this analysis, including its *post hoc* nature and that the analysis was not powered to assess differences in efficacy outcomes by different stages of lung function. In addition, it is likely that the ASCEND and CAPACITY population had less severe dyspnoea than might

be expected in a real-world population. For example, the INSIGHTS-IPF registry reported much higher UCSD SOBQ scores at baseline [14] than were reported in the pirfenidone trials, which may be due to the exclusion criteria for those trials.

In conclusion, these results suggest that treatment with pirfenidone slowed the worsening of patient-reported breathlessness over 12 months versus placebo in patients with GAP Stage II/III or percent predicted FVC <80%. Further research is needed to examine the effects of pirfenidone on IPF-related symptoms including dyspnoea in real-world populations. There is also a need to confirm if the change in UCSD SOBQ over time is valid in a real-world population of patients with IPF.

Data sharing: Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Competing interests:

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FG and KUK are employees of F. Hoffmann-La Roche, Ltd and may hold shares.

UP was an employee of Clinipace-Accovion GmbH – a company contracted by F. Hoffmann-La Roche, Ltd. to perform analyses of study data – at the time of this study.

CA has received personal fees from FibroGen, Bayer, Boehringer Ingelheim, GlaxoSmithKline, InterMune/F. Hoffmann-La Roche, Ltd., Merck Sharp & Dohme Corp., and Sanofi.

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Figure 1 Median change in UCSD SOBQ scores from baseline over time in patients a) with GAP Stage I versus GAP Stage II/III and b) with percent predicted FVC ≥80% versus <80%. Missing values were imputed using the sum of squared differences method. Deaths were imputed to a score of 120 points and p-values are for the Wilcoxon two-sample test. Categorical changes in UCSD SOBQ scores in patients c) with GAP Stage II/III and d) with percent predicted FVC <80%. Missing values were imputed using the sum of squared differences method. Deaths were assigned to the group with a ≥30-point change in UCSD SOBQ at Month 12. p-values are for pirfenidone versus placebo across categories (Mantel-Haenszel chi-squared test).

[#]n=375, pirfenidone; n=381, placebo; [¶]n=473, pirfenidone; n=450, placebo.

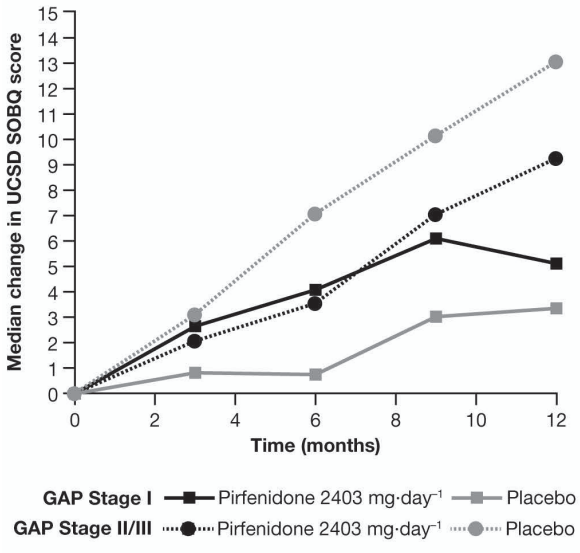
%FVC, percent predicted forced vital capacity; CI, confidence interval; GAP, Gender, Age, Physiology; HL, Hodges-Lehmann; IQR, interquartile range; UCSD SOBQ, University of California, San Diego Shortness of Breath Questionnaire.

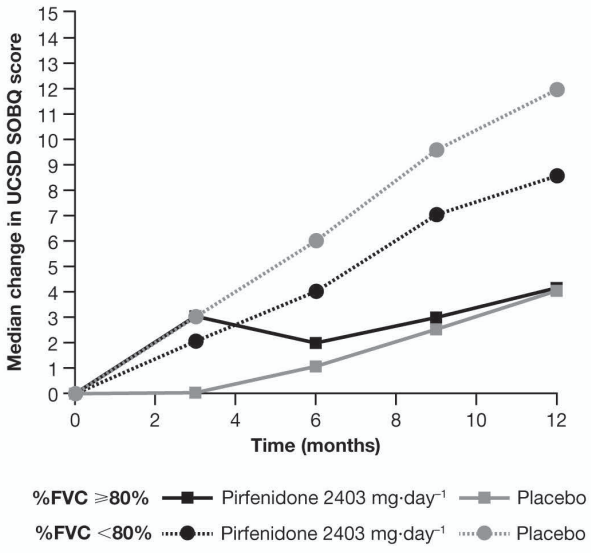
a)

UCSD SOBQ at 12 months	GAP Stage I		GAP Stage II/III	
	Pirfenidone (n=242)	Placebo (n=234)	Pirfenidone (n=375)	Placebo (n=381)
Score at baseline, median (IQR)	28.9 (13.5–44.0)	30.4 (16.0–48.0)	33.4 (19.5–51.0)	32.5 (19.0–51.1)
Median change from baseline	5.0	3.3	9.2	13.0
HL median difference in change (95% CI)	0.11 (–2.50, 3.00) p=0.852		–3.67 (–6.50, –1.00) p=0.009	

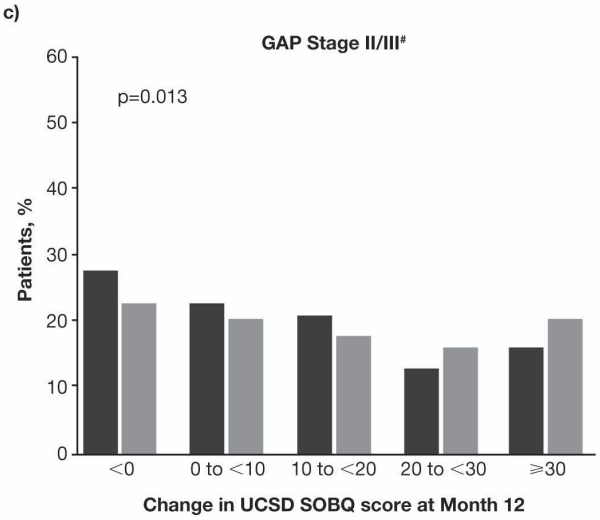
b)

UCSD SOBQ at 12 months	%FVC ⩾80%		%FVC <80%	
	Pirfenidone (n=144)	Placebo (n=167)	Pirfenidone (n=473)	Placebo (n=450)
Score at baseline, median (IQR)	25.0 (10.0–43.6)	29.0 (15.0–44.0)	33.0 (19.0–50.0)	32.0 (18.5–51.1)
Median change from baseline	4.1	4.0	8.5	12.0
HL median difference in change (95% CI)	0.18 (–3.00, 3.50) p=0.876		–3.50 (–6.00, –1.00) p=0.006	

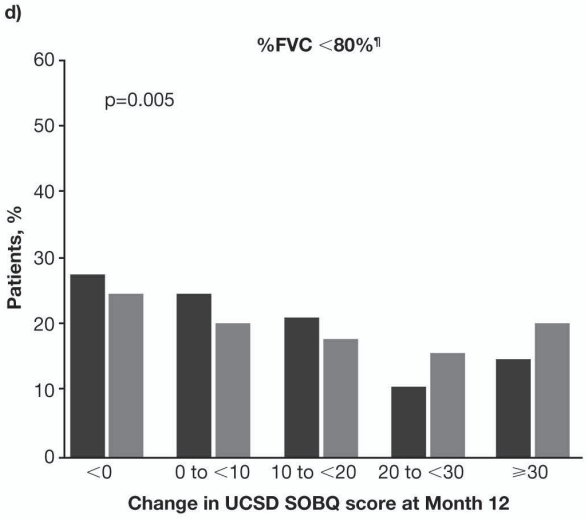




c)



d)



■ Pirfenidone 2403 mg·day⁻¹ ■ Placebo