Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefiting from treatment

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Abstract

Background: A phase III trial in Japan showed that pirfenidone is effective for idiopathic pulmonary fibrosis (IPF). To find out which patients specifically benefit from pirfenidone, we analyzed in an exploratory manner the data from the phase III trial.

Methods: The patients in the phase III trial were stratified by baseline percentage predicted vital capacity (%VC), arterial oxygen partial pressure (PaO2), and the lowest oxygen saturation by pulse oximetry (SpO2) during the 6-minute steady-state exercise test (6MET). In the subpopulations, changes in VC and subjective symptoms (cough and dyspnea on the Fletcher, Hugh-Jones [F, H-J] Classification scale) were evaluated in patients treated with high-dose (1800 mg/day) pirfenidone, low-dose (1200 mg/day) pirfenidone, and placebo at week 52.

Results: Significant efficacy of pirfenidone in reducing the decline in VC could be seen in a subpopulation having %VC ≥ 70% and SpO2 < 90% at baseline. This favorable effect was accompanied by categorical change in VC and progression-free survival time. In the subpopulation, pirfenidone significantly suppressed cough and dyspnea.

Conclusions: IPF patients having %VC ≥ 70% and SpO2 < 90% at baseline will most likely benefit from pirfenidone when evaluated using changes in VC (and %VC), and cough and dyspnea symptoms. This subpopulation could expect to benefit most from pirfenidone treatment.

Trial Registration: This clinical trial was registered with the Japan Pharmaceutical Information Center (JAPIC) on September 13th, 2005 (Registration Number: JAPICCTI-050121).

Background

Idiopathic pulmonary fibrosis (IPF) is a fatal, progressive fibrotic lung disease with a median survival of 3-5 years and no proven effective therapy to date [1,2]. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone; Shionogi & Co., Ltd., Osaka, Japan; Marnac Inc., Dallas, TX, USA) [3-7] is an antifibrotic drug for IPF which has combined anti-inflammatory, antioxidant, and antifibrotic effects in experimental models of pulmonary fibrosis [8-12]. A randomized, double-blind, placebo-controlled phase II trial of pirfenidone with 107 Japanese IPF patients demonstrated that pirfenidone significantly reduced the decline in vital capacity (VC) at week 36 compared to placebo (p = 0.037) [7]. These encouraging results prompted us to undertake a phase III clinical trial with 275 Japanese patients. In the Phase III trial, pirfenidone showed significant reduction in the decline of VC at week 52 (p = 0.042) and improved progression-free survival (PFS) time (p = 0.028) [13]. These Phase II and III data led to regulatory approval of pirfenidone in Japan for the treatment of IPF in 2008.
The Phase II trial in Japan also led to two larger, international, randomized trials of pirfenidone for IPF (CAPACITY, study 004 and study 006 with 435 and 344 IPF patients, respectively) [14]. In study 004, the decline in percentage predicted forced vital capacity (FVC) at week 72 was significantly reduced in pirfenidone-treated patients compared to those treated with placebo (p = 0.001). In study 006, the difference in FVC change at week 72 was not significant. However, the decline in % FVC was reduced at all time points during the first year. An analysis of pooled data from the two studies supported the treatment effect of pirfenidone on the %FVC, PFS time, and 6-minute walk test (6MWT) distance. In February 2011, pirfenidone was granted marketing authorization by the European Commission for the treatment of IPF.

Extended analyses of the phase III trial data in Japan revealed a subgroup of patients who benefited from pirfenidone. Ebina et al. [15,16] examined the association between pirfenidone efficacy (changes in VC at week 52) and the baseline %VC, and reported that pirfenidone was more effective in patients with relatively mild impairment of lung function (%VC ≥ 70).

To clarify more precisely which patients specifically benefit from pirfenidone, we examined the association between pirfenidone efficacy and the baseline lung functions including %VC, arterial oxygen partial pressure (PaO2), and the lowest oxygen saturation in the 6-minute steady-state exercise test (the lowest SpO2). In each subgroup, the change in VC, PFS time, and subjective symptoms (cough and dyspnea on the Fletcher, Hugh-Jones [F, H-J Classification scale] were evaluated after high-dose (1800 mg/day) pirfenidone, low-dose (1200 mg/day) pirfenidone, and placebo treatment for 52 weeks.

Methods

Overall Design

The phase III trial in Japan was a multicenter, double-blind, randomized, placebo-controlled trial. The diagnosis of IPF was in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Consensus statement [17] and the “Clinical diagnostic criteria for idiopathic interstitial pneumonia (IIP)” (4th edition) in Japan [18]. Patients received either high-dose pirfenidone (1800 mg/day), low-dose pirfenidone (1200 mg/day), or placebo for 52 weeks.

The trial was conducted in accordance with the principles laid down in the Declaration of Helsinki (2002 version). The protocol was approved by the institutional review board at each center and the written informed consent was obtained from all participants prior to enrollment. The ongoing efficacy and safety results were reviewed by the independent Data and Safety Monitoring Board (DSMB).

Inclusion criteria

Eligible patients were adults (20-75 years old) with IPF diagnosed on the basis of the above criteria and meeting the following SpO2 criteria: 1) oxygen desaturation of >5% difference between the resting SpO2 and the lowest SpO2; 2) lowest SpO2 of ≥85% while breathing air.

Patients and randomization

In all, 325 patients were screened at 73 centers in Japan, and 275 patients were randomized to one of three treatment groups (i.e., the high-dose, low-dose, and placebo groups) at a ratio of 2:1:2. Ultimately, 267 (108, 55, and 104 patients in high-dose, low-dose and placebo groups, respectively) were evaluated for the efficacy as the full analysis set (FAS). Eight patients were excluded for having no post-baseline data.

Measurements

The measurements of VC, the lowest SpO2, PaO2 at rest, and subjective symptoms (cough and dyspnea intensity rated using the F, H-J classification system [19]) were defined as in our previous report [13]. The cough severity was rated either 1 [none; no cough], 2 [mild; intermittent cough], 3 [moderate; irritating, but not debilitating cough], and 4 [heavy; debilitating cough characterized by shortness of breath and exhaustion]. Progression-free survival (PFS) was defined by death and/or ≥10% decline in VC from baseline. VC was measured every 4 weeks, while the lowest SpO2 and other pulmonary function tests were observed every 12 weeks. In this trial, the primary endpoint was the change in VC. As the secondary endpoints, we used: 1) PFS time and 2) change in the lowest SpO2 during the 6-minute steady-state exercise test (6MET). Initially, the primary endpoint was the lowest SpO2 during the 6MET, as in the phase II trial [7]. Then, as explained in our previous report [13], a decision was made to change the primary endpoint to VC prior to breaking the code, in accordance with the recommendation of the DSMB.

Statistical analysis

To identify the subpopulation that benefited most from pirfenidone treatment, we stratified the patients from the phase III trial using 70% of baseline %VC or 70 torr of baseline PaO2 and 90% of baseline SpO2 as boundary values. Namely, patients were stratified by baseline %VC (<70 vs ≥70%) or PaO2 (<70 vs ≥70) and the lowest SpO2 (<90 vs ≥90%). We selected these boundary values based on the results of the phase II trial in Japan and exploratory examination of the phase III trial by Ebina et al. [15]. Following analyses were performed in each of the subpopulations. Means of the changes in VC and %VC from baseline were compared between the treated...
(pirfenidone high-dose and low-dose) and placebo groups with the analysis of covariance (ANCOVA) using the respective baseline measurements as covariates. In the ANCOVA, the principle of the last observation carried forward (LOCF) was adopted to impute missing values. The cumulative PFS rates were estimated using the Kaplan-Meier method and the distributions of PFS time were compared using the log-rank test. ANCOVA was used to compare the means of the changes in subjective symptoms (i.e., cough and dyspnea scored on the F, H-J classification scale) between groups treated with either high- or low-dose pirfenidone or placebo. In these exploratory analyses, the significance level of tests was set at 0.1 (two-sided), inasmuch as 0.1 was the level used in the phase III study [13].

**Results**

The phase III trial showed that pirfenidone reduced the decline in VC at week 52 in IPF patients, and significantly prolonged the PFS time, compared to placebo [13]. In this exploratory analysis, patients were grouped by baseline %VC or PaO2 at rest and the lowest SpO2 to identify the subpopulations that benefited most from pirfenidone treatment. Specifically, patients were stratified on the basis of %VC (<70 vs ≥70), PaO2 (<70 vs ≥90), and the lowest SpO2 (<90 vs ≥90).

The changes in VC and %VC in subpopulations stratified by baseline %VC, PaO2, and the lowest SpO2 When patients were stratified by baseline %VC (<70%, ≥70%) and the lowest SpO2 (<90, ≥90), pirfenidone tended to be more effective in patients with baseline %VC ≥70 and the lowest SpO2 <90 (Subgroup A) than in the other subgroups. Namely, in Subgroup A, mean declines in VC and %VC at week 52 (all p-values <0.1; Table 1) and the distribution of progression-free survival times (data not shown) were significantly different between those treated with pirfenidone (high-dose, low-dose, and high+low dose) and those treated with placebo. When patients were stratified by PaO2 (<70, ≥70) and by SpO2 on exertion (<90, ≥90), pirfenidone tended to be more effective in patients with PaO2 ≥70 and SpO2 on exertion <90 (Subgroup B) than in the other subgroups. P-values of the comparisons of mean declines in VC (%VC) between the treatment groups (pirfenidone high-dose, low-dose, and high+low dose) and the placebo group were 0.151 (0.198), 0.088 (0.097) and 0.059 (0.074), respectively (Table 2). In Subgroup B, a similar trend was seen in progression-free survival time (data not shown).

Incidentally, in the phase II trial in Japan, the change in VC was categorized as “improved,” “stable,” or “deteriorated” in accordance with the ATS/ERS criteria [17] (where separation into three categories was based on 10% change in VC). The categorical change was significantly different between the pirfenidone treatment group and placebo group in the phase II trial but not in the phase III trial as described in the Online Supplementary Materials of our preceding paper [13]. By the way, patients in Subgroup B met the criteria for entry into the phase II trial, and Subgroup B was expected to resemble Subgroup A. Therefore, it was expected that significant differences might be seen by comparing categorical changes in Subgroup A and/or Subgroup B. Thus, the distributions of categorical changes in VC at week 52 were compared between pirfenidone (high- and low-dose) and placebo groups with the Wilcoxon rank sum test in “Subgroup A” and “Subgroup B” of the phase III trial. Then, changes in VC were classified as “improved,” “stable,” or “deteriorated” using the 10% change criterion employed in the Phase II trial. The differences in the distribution of categorical change in VC

| Table 1 Decline in VC and %VC at week 52 in subpopulations characterized by baseline %VC and the lowest SpO2 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Item            | Category 1 SpO2 | Category 2 Baseline %VC | High-dose Group | Low-dose Group | Placebo Group | P-value |
|                 |                 |                             | LS mean (n) | SE | LS mean (n) | SE | LS mean (n) | SE | H vs P | L vs P | H+L vs P |
| Change in VC    | 6MWT SpO2≥90    | %VC≥70                      | -0.072 (35) | 0.033 | -0.004 (16) | 0.050 | -0.090 (32) | 0.035 | 0.7035 | 0.3195 | 0.2581 |
|                 |                 | %VC<70                      | -0.263 (9) | 0.073 | -0.185 (6) | 0.090 | -0.225 (9) | 0.073 | 0.7181 | 0.7350 | 0.9919 |
| Change in %VC   | 6MWT SpO2≥90    | %VC≥70                      | -0.050 (36) | 0.049 | -0.016 (17) | 0.071 | -0.199 (36) | 0.049 | 0.0359 | 0.0372 | 0.0131 |
|                 |                 | %VC<70                      | -0.148 (23) | 0.051 | -0.181 (15) | 0.062 | -0.168 (26) | 0.048 | 0.7768 | 0.8735 | 0.9539 |
| Change in VC    | 6MWT SpO2<90    | %VC≥70                      | -2.083 (35) | 1.070 | -0.420 (16) | 1.580 | -2.801 (32) | 1.114 | 0.6438 | 0.2209 | 0.2927 |
|                 |                 | %VC<70                      | -0.984 (9) | 2.446 | -7.340 (6) | 2.963 | -7.167 (9) | 2.449 | 0.5902 | 0.9647 | 0.7427 |
| Change in %VC   | 6MWT SpO2<90    | %VC≥70                      | -1.737 (36) | 1.569 | -0.590 (17) | 2.264 | -6.080 (36) | 1.568 | 0.0555 | 0.0493 | 0.0213 |
|                 |                 | %VC<70                      | -4.143 (23) | 1.637 | -5.090 (15) | 2.079 | -5.669 (26) | 1.567 | 0.5037 | 0.8280 | 0.6158 |
were statistically significant between high-dose and placebo groups (p = 0.0691), low-dose and placebo groups (p = 0.0861), and pooled (high + low) dose and placebo groups in Subgroup A (p = 0.0295; Figure 1) but not in “Subgroup B” (data not shown).

To evaluate the changes in subjective symptoms (i.e., cough and dyspnea) during the phase III trial, means of the changes in cough score and dyspnea score (with F,

| Item          | Category 1 SpO2 Category 2 PaO2 | High-dose Group | Low-dose Group | Placebo Group | P-value |
|---------------|---------------------------------|-----------------|----------------|---------------|---------|
| Change in VC  | 6MWT SpO2≥90                    | PaO2≥70 Torr    | -0.115 (43) SE 0.032 | -0.060 (22) SE 0.045 | -0.137 (36) SE 0.035 | 0.6423 0.1766 0.2667 |
|               | PaO2<70 Torr                    | -0.014 (15) SE 0.067 | -0.102 (28) SE 0.129 | -0.135 (6) SE 0.105 | 0.3456 0.8456 0.5556 |
| Change in %VC | 6MWT SpO2≥90                    | PaO2≥70 Torr    | -3.486 (43) SE 1.013 | -2.329 (22) SE 1.412 | -4.544 (36) SE 1.107 | 0.4833 0.2200 0.2484 |
|               | PaO2<70 Torr                    | -0.204 (15) SE 2.040 | -3.038 (4) SE 3.951 | -3.964 (6) SE 3.229 | 0.3364 0.8578 0.5568 |

(-; not calculated.)

Temporal changes of subjective symptoms in subpopulations

To evaluate the changes in subjective symptoms (i.e., cough and dyspnea) during the phase III trial, means of the changes in cough score and dyspnea score (with F,
H-J classification) from baseline were calculated at each observation time and are shown in Figures 2 and 3. Further, the results of ANCOVA using the changes in cough and dyspnea scores from baseline to week 52 as responses, also are shown in Figures 2 and 3, respectively. In the full analysis set (FAS), pirfenidone tended to prevent the elevation of these scores more consistently in the high-dose and low-dose groups than in the placebo group, although the differences were not significant. When examined in Subgroups A and B, changes in cough and dyspnea scores showed that pirfenidone prevented increase in cough (Figure 2) and dyspnea (Figure 3).

Figure 2 Temporal changes in cough score in subpopulations. A) Full analysis set (FAS; all patients), B) Subgroup A [%VC ≥ 70 and the lowest SpO2 < 90], and C) Subgroup B [PaO2 ≥ 70 and the lowest SpO2 < 90]. Data are shown as mean ± SE. High-dose (solid line); low dose (dashed line); placebo (dashed line in bold). The mean changes from baseline to week 52 were compared between high (or low-dose) and placebo groups with ANCOVA.
3) more effectively in Subgroups A and B than in the FAS at week 52. In addition, the differences in dyspnea scores seen in Subgroup A between pirfenidone (high- and low-dose) and placebo groups were significant at week 12 (p-values were 0.0428 and 0.0379, respectively). The significant difference in cough score in Subgroup A was seen between low-dose and placebo group (p = 0.0502).

Figure 3 Temporal changes in dyspnea score (F, H-J classification) in subpopulations. A) Full analysis set (FAS; all patients), B) Subgroup A \([\text{FVC} \geq 70 \text{ and SpO2 during 6MET} < 90]\), and C) Subgroup B \([\text{PaO2} \geq 70 \text{ and SpO2 during 6MET} < 90]\). Data are shown as mean ± SE. High-dose (solid line); low dose (dashed line); placebo (dashed line in bold). The mean changes from baseline to week 52 were compared between high or low-dose and placebo groups with ANCOVA.
Discussion

Our exploratory analyses using changes in VC, categorical changes in VC, PFS time, and scores on subjective symptoms as outcomes suggested that pirfenidone was more effective in patients with mild-to-moderate lung function impairment (baseline %VC ≥ 70 and the lowest SpO2 < 90; Subgroup A). In addition, pirfenidone had significant effects on some of these outcomes in Subgroup B (baseline PaO2 ≥ 70 and the lowest SpO2 < 90). In the population of patients with mild-to-moderate disease, pirfenidone is especially effective in patients with desaturation during exercise which typically corresponds to the lowest baseline SpO2 < 90.

To evaluate temporal changes in subjective symptoms in the phase III trial, means of the changes in cough (data not shown). Although the difference was not statistically significant was lower than that in the placebo group (8.33% [3/36]), the incidence in the pirfenidone group (1.82% [1/55]) was significantly lower compared to the placebo group in Subgroup A. These characteristics were similar in patients enrolled in the phase II trial and in the Subgroup B patients of the phase III trial were broader (i.e., 1] oxygen desaturation of >5% difference between resting SpO2 and the lowest SpO2, and 2] the lowest SpO2 >85% while breathing air). These characteristics were similar in patients enrolled in the phase II trial and in the Subgroup B patients of the phase III trial enrolled in this study. Pirfenidone was shown to have a more marked effect on both the patients with the lowest SpO2 ≤ 90% in Subgroup B as those in the phase II trial (data not shown). Possibly, the phase II trial might have enrolled a population of patients who were more responsive to the drug. The broader criteria for inclusion into the phase III trial might have resulted in a more heterogeneous population and more variable data.

In Japan, the severity of idiopathic interstitial pneumonia (IIPs) is classified on the basis of baseline PaO2 value at rest, and categories are defined by 10-torr intervals. The grade of IIPs in patients with PaO2 of < 90 on exertion is increased by one (except for grade 1) as described in the online supplemental materials of our previous report of the Phase III trial [13]. In the phase III trial, patients were grouped based on severity to identify the subpopulation that was more responsive to pirfenidone. Pirfenidone was found to be more effective in grade-III patients (data not shown). A more detailed analysis revealed that the population of patients with PaO2 ≥ 70 and < 80 included many grade-III patients.
when SpO₂ was < 90% on exertion (data not shown). These findings also may support the efficacy of pirfenidone in patients with desaturation during exercise.

Identifying those patients clinically responsive to pirfenidone is very important. The present analyses revealed that pirfenidone was more effective in populations of patients with relatively favorable baseline %VC and PaO₂, especially in those with desaturation on exertion. Since pirfenidone was more effective in Subgroup A than in Subgroup B, baseline %VC may be a more appropriate index than PaO₂. In addition, patients presenting desaturation during exercise may be comparable to those complaining of dyspnea on exertion. For more beneficial use of pirfenidone, the factors—baseline %VC and the presence/absence of complaints of dyspnea on exertion—may be used to select candidate patients. However, since responsiveness in this study depended on the stage of the disease as determined by respiratory function tests, these factors cannot be regarded as indicative of a responsive phenotype but rather as indicative of a responsive “phenostage” (coined by the authors). (A ‘Phenotype’ determining response to therapy, for example to anti-cancer therapy, is generally characterized by expression of a specific gene, whereas the ‘responsiveness’ of the subgroup identified in this study may be due to the timing of treatment during disease progression rather than a specific gene.) A sub-analysis of data from the CAPACITY trials [14] yielded similar results. The FVC change at week 72 showed that a subgroup of patients given oxygen during 6MWT at baseline responded favorably to pirfenidone [22]. To determine whether this observation and our findings are equivalent, a detailed sub-analysis of data from the CAPACITY trials or further prospective studies will be needed.

To support the results obtained from the analyses described in preceding sections, we used respiratory function tests at baseline to determine the factors associated with the efficacy of pirfenidone. Thus, we included percentage predicted total lung capacity (%TLC), %DLco in addition to the lowest SpO₂, %VC, and PaO₂. Then, we used the change in VC from baseline to week 52 as the efficacy parameter and evaluated the effects of the 5 function tests on this efficacy parameter in pirfenidone and placebo groups. At first, correlation coefficients among the 5 respiratory tests were calculated in the pirfenidone and placebo groups. The correlation coefficients between %VC and %TLC were very high in both groups (0.811 and 0.826, respectively). Thus, we subsequently omitted %TLC from the evaluation, and retained %VC since %VC behaves like VC (which was the primary endpoint in the phase III trial) and was considered indispensable in the additional analysis. Then, we applied a multiple regression model letting the change in VC serve as the response variable and the four respiratory function tests as explanatory variables in the two groups (Table 3). From the Tables, the regression coefficient of %VC in the pirfenidone group was significant (p = 0.0018), and it was suggested that in patients with relatively low baseline %VC, the tendency to prevent the decline in VC was greater in the pirfenidone group than in the placebo group.

Further, three dichotomized variables (the lowest SpO₂, %VC, and PaO₂ with boundary values of 90%, 70%, and 70 torr, respectively) were used in the stratification, and the effects of the variables on the change in VC were evaluated with a multiple regression model. In the pirfenidone group, the coefficients of %VC and PaO₂ were significant (p-values, 0.0002 and 0.0483, respectively, see Table 4). In the placebo group, the coefficients were not significant. This seems to support the findings presented in the previous sections, namely that the most favorable response to pirfenidone relative to placebo was in patients with %VC ≥70% and SpO₂ <90 (Subgroup A). Notably, when patients were stratified using 70% as the boundary value of %VC, decline in VC was reduced in patients with %VC ≥70 after pirfenidone treatment but not after placebo treatment. In addition, although the coefficient of SpO₂ was not significant, the decline of VC in patients with SpO₂ <90% tended to be relatively small in the pirfenidone group and large in the placebo group. Accordingly, patients with %VC ≥70% and SpO₂ <90 (Subgroup A) received more benefit from pirfenidone than did other patients. For patients with PaO₂ ≥70% and <70, the change in VC differed less between the pirfenidone and placebo groups as indicated by the negative signs of both regression coefficients of the dichotomized PaO₂. Therefore, it was suggested that efficacy of pirfenidone was less clear in Subgroup B than in Subgroup A.

Limitations
Given the exploratory nature of our study, limitations include post-hoc analysis and small sample size due to

| Table 3 Effects of respiratory tests on the change in VC in Pirfenidone and Placebo groups |
|---------------------------------|---------|-------|-------|-------|
| Group                      | Parameter | Estimate | S.E.  | t-value | p-value |
| Pirfenidone                 | Intercept | -0.3543 | 0.7428| -0.48   | 0.6340 |
| (n = 155)                   | The lowest SpO₂ | 0.0029 | 0.0091| 0.32   | 0.7514 |
|                             | %VC      | 0.0035 | 0.0011| 3.17   | 0.0018 |
|                             | %DLco    | -0.0011| 0.0011| -0.97  | 0.3361 |
|                             | PaO₂     | -0.0025| 0.0021| -1.19  | 0.2378 |
| Placebo                     | Intercept | -2.0951| 1.2726| -1.65  | 0.1029 |
| (n = 102)                   | The lowest SpO₂ | 0.0217 | 0.0146| 1.48   | 0.1412 |
|                             | %VC      | 0.0008 | 0.0017| 0.49   | 0.6279 |
|                             | %DLco    | -0.0017| 0.0017| -0.99  | 0.3248 |
|                             | PaO₂     | 0.0003 | 0.0033| 0.10   | 0.9172 |

(%TLC was omitted from the evaluation)
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Table 4 Effects of respiratory function tests (values dichotomized) on the change in VC in pirfenidone and placebo groups

| Group          | Parameter  | Estimate | S.E.  | t-value | p-value |
|----------------|------------|----------|-------|---------|---------|
| Pirfenidone    | Intercept  | -0.0057  | 0.0523 | -1.64   | 0.1039  |
| (n = 155)      | The lowest SpO₂ < 90 vs ≥ 90 | -0.0090  | 0.0381 | -0.24   | 0.8133  |
|                | %VC: <70 vs ≥ 70 | 0.1447  | 0.0386 | 3.75    | 0.0002  |
|                | PaO₂: <70 vs ≥ 70 | -0.1111 | 0.0558 | -1.99   | 0.0483  |
| Placebo        | Intercept  | -0.1196  | 0.0923 | -1.30   | 0.1982  |
| (n = 103)      | The lowest SpO₂ < 90 vs ≥ 90 | 0.0628  | 0.0566 | 1.11    | 0.2701  |
|                | %VC: <70 vs ≥ 70 | 0.0302  | 0.0585 | 0.52    | 0.6067  |
|                | PaO₂: <70 vs ≥ 70 | -0.0977 | 0.0878 | -1.11   | 0.2685  |

dyspnea. It is suggested that this subpopulation, especially, will benefit from pirfenidone treatment.

Abbreviations used in this paper
IPF: idiopathic pulmonary fibrosis; VC: vital capacity; PFS: progression-free survival; SpO₂: oxygen saturation by pulse oximetry; %DLco: % diffusing capacity of the lung for carbon monoxide; %TLC: % predicted total lung capacity; FAS: full analysis set; PFT: pulmonary function test; 6MET: 6-minute steady-state exercise test; ANCOVA: analysis of covariance; LOCF: last observation carried forward; ATS: American Thoracic Society; ERS: European Respiratory Society; F: H-J, Fletcher,Hugh-Jones; DSMB: Data and Safety Monitoring Board.

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