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# Pirfenidone in idiopathic pulmonary fibrosis:

# A phase III clinical trial in Japan

H. Taniguchi[1)], M. Ebina[2)], Y. Kondoh[1)], T. Ogura[3)], A. Azuma[4)], M. Suga[5)], Y. Taguchi[6)], H. Takahashi[7)], K. Nakata[8)], A. Sato[9)], M. Takeuchi[10)], G. Raghu[11)], S. Kudoh[4)], T. Nukiwa*[2)], and Pirfenidone Clinical Study Group in Japan

(1) Dept of Respiratory Medicine and Allergy, Tosei General Hospital, Aichi (2) Dept of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, (3) Dept of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, (4) Fourth Dept of Internal Medicine, Nippon Medical School, Tokyo(5) Dept of respiratory medicine, Saiseikai Kumamoto Hospital, Kumamoto, (6) Dept of Respiratory Medicine, Tenri Hospital, Tenri, (7) Third Dept of Internal Medicine, Sapporo Medical University Hospital, Sapporo, (8) Nakata clinic, Tokyo, (9) Kyoto Preventive Medical Center, Kyoto (10) Dept of Biostatistics, Kitasato University, Tokyo and (11) University of Washington Medical Center, Seattle, WA, USA

***CORRESPONDENCE**

T. Nukiwa, M.D.

Professor, Department of Respiratory Medicine,

Tohoku University Graduate School of Medicine,

Sendai 980-8574, Japan

Telephone: +81-22-717-8534, FAX: +81-22-717-8549

E-mail: toshinkw@idac.tohoku.ac.jp

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## ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease without proven effective therapy. A multi-centered, double-blind, placebo-controlled, randomized phase III clinical trial was conducted in Japanese patients with well-defined IPF to determine the efficacy and safety of pirfenidone, a novel antifibrotic, oral agent, over 52 weeks. Of total 275 patients randomized [high-dose (1800 mg/day), low-dose (1200 mg/day), or placebo group (2:1:2)], 267 patients were evaluated for the efficacy of pirfenidone. Prior to unblinding, the primary endpoint was revised; the change in vital capacity (VC) was assessed at week 52. Secondary endpoints included the progression-free survival (PFS) time. Significant differences were observed in the decline of VC, (primary endpoint) between Placebo group (-0.16 liter) and High-dose group (-0.09 liter) ($p=0.0416$); and in the secondary endpoint, the PFS, between the two groups ($p=0.0280$). Although photosensitivity, a well established side effect of pirfenidone, was the major adverse event in this study, it was mild in severity in most of the patients. Pirfenidone was relatively well tolerated in patients with IPF. Treatment with pirfenidone may decrease the rate of decline in VC and may increase the PFS time over 52 weeks. Additional studies are needed to confirm these findings.

KEYWORDS: Pirfenidone, idiopathic pulmonary fibrosis, vital capacity, progression-free survival time.

## INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a devastating, progressive fibrotic lung disease with a median survival of 3–5 years without proven effective therapy [1, 2]. Recent studies have suggested that IPF develops from chronic epithelial cell injury and aberrant activation of progressive fibrosis [3, 4]. Therefore, the therapeutic strategy against IPF has shifted from corticosteroids and/or immunosuppressants to antifibrotic agents, as reported in recent clinical trials [5, 6].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone; Shionogi & Co., Ltd., Osaka, Japan; MARNAC Inc., Dallas, TX, USA) [7, 8] is a promising agent with therapeutic potential for IPF that has combined anti-inflammatory, antioxidant, and antifibrotic effects in experimental models of pulmonary fibrosis [9-14]. Following an open label phase II pioneer study [7], a double-blind, placebo-controlled clinical trial of pirfenidone in Japanese patients with IPF demonstrated a lesser decline of vital capacity (VC) in patients receiving pirfenidone for 9 months [15]. The trial was prematurely terminated by the independent Data and Safety Monitoring Board (DSMB) because of a higher incidence of acute exacerbations in the placebo group than the pirfenidone group. These encouraging results, prompted us to undertake a phase III one-year-long clinical study to examine the therapeutic effects of pirfenidone on lung functional deterioration and disease progression in patients with IPF.

## MATERIALS AND METHODS

### Study subjects

The diagnosis of IPF was in accordance with the American Thoracic Society/European Respiratory Society Consensus statement [16] and 4$^{th}$ version of the guideline of clinical diagnostic criteria for idiopathic interstitial pneumonia in Japan [17]. The high-resolution computed tomography (HRCT) scans of chest were reviewed by expert chest radiologists prior to randomization; two out of six expert radiologists independently evaluated the HRCT images to agree and determine whether the pattern of usual interstitial pneumonia (UIP) was present or not in accordance with the predetermined protocol (online supplement). In cases of disagreement, the interpretation of the third radiologist favored the final decision, and the diagnosis of patients with probable UIP pattern on HRCT was confirmed by the presence of histopathologic UIP pattern in surgical lung biopsy samples.

Eligible patients were adults (20 to 75 years old) with IPF diagnosis based on above criteria and meeting the following $SpO_2$ criteria: 1) demonstrate oxygen desaturation of >5% difference between resting $SpO_2$ and the lowest $SpO_2$ during a 6-minute steady-state exercise test (6MET), and 2) the lowest $SpO_2$ during the 6MET >85% while breathing air. The 6MET procedure was in accordance to previously study protocol (online supplement). Exclusion criteria were (1) a decrease in symptoms during the preceding six months, (2) use of immunosuppressants and/or oral corticosteroids at a dose of more than 10 mg/day during the preceding three months, (3) clinical features of idiopathic interstitial pneumonia other than IPF, (4) evidence of known coexisting pulmonary hypertension, asthma, tuberculosis, bronchiectasis, aspergillosis, or severe respiratory infection.

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 DSMB.

## Study design

This study was a multi-centered, double-blind, randomized, placebo-controlled, phase III clinical trial designed to determine the efficacy and safety of oral administration of pirfenidone for one year in patients with IPF. Eligible patients were allocated into three groups: High-dose (1800 mg/day) group, Low-dose (1200 mg/day) group, and Placebo group, at the ratio of 2:1:2, respectively, with a modified minimization method including a few steps of random allocation based on the idea of biased coin design to balance baseline $SpO_2$ [18, 19].

## Treatment Regimen

Pirfenidone 200 mg tablet and matching placebo were provided for oral use by Shionogi & Co., Ltd. (Osaka, Japan). The dose was increased in a stepwise manner as follows: one tablet *t.i.d* orally administered for the first two weeks (600 mg/day in High-dose, 600 mg/day in Low-dose, and 0 mg/day in Placebo groups), then two tablets per dose *t.i.d.* for the following two weeks (1200 mg/day in High-dose, 600 mg/day in Low-dose, and 0 mg/day in Placebo groups), and three tablets *t.i.d.* for the remaining 48 weeks (1800 mg/day in High-dose, 1200 mg/day in Low-dose, and 0 mg/day in Placebo groups) (online supplement). While concomitant use of corticosteroid $\leq$10 mg/day (as the prednisone equivalent) was permitted during the study period, concomitant use of immunosuppressants and other experimental agents under investigation was not allowed (online supplement). All participants were forewarned regarding the potentials of photosensitivity skin rash and were advised to use sunscreens during exposure to direct sunlight.

## Efficacy Endpoints

The primary endpoint was the change in VC from baseline to Week 52.

Secondary endpoints were PFS time and the change in the lowest $SpO_2$ during 6MET. The progression of disease was defined by death and/or >10% decline in VC from baseline. When the data of VC could not be obtained due to worsening of respiratory symptoms including acute exacerbation, the case was also classified as the progression of the disease. As in the phase II study conducted in Japan [15], the procedure of 6MET was prespecified in the protocol (online supplement). Tertiary endpoints were pulmonary function tests (PFTs; $PaO_2$, $AaDO_2$ at rest, TLC and DLco), acute exacerbation [20], serum levels of the markers of interstitial pneumonias (KL-6, SP-D and SP-A; online supplement) and subjective/objective symptoms (cough, presence/absence of sputum and Hugh-Jones classification).

VC was measured every 4 weeks, while the lowest $SpO_2$ during the 6MET and other PFTs were determined every 12 weeks. Acute exacerbation of IPF was defined according to the previous reports and revised criteria for acute exacerbation of IPF in Japan [15, 20] (see appendices in online supplement).

The change in the lowest $SpO_2$ during 6MET over 52 weeks was the original intended primary endpoint for this study. This was recommended by the independent DSMB, prior to breaking the code. The decision was made to revise the primary endpoint from the lowest $SpO_2$ to VC at Week 52 and assess the change in the lowest $SpO_2$ during the 6MET as a secondary endpoint. This decision was based on the evolved knowledge of assessment with objective measurements in IPF [21-26] as well as the lack of validation in the 6 MET study (unpublished data) and difficulties in reproducibility of the SpO2 measurements during 6 minute walk test [27].

## Statistical Analysis

The planned sample size was 250 in total; 100, 50 and 100 patients in the High-dose, Low-dose, and Placebo groups, respectively. The sample sizes of 100 for the High-dose and Placebo groups were determined based on simulations that would

provide statistical power of 0.8 to detect assumed differences of the mean changes in the lowest SpO2 from baseline to Week 52 between the two groups at a significance level in this study of 0.1 (two-sided) (the details in online supplement). Although the primary endpoint was altered from the lowest $SpO_2$ to VC after the study was started, the power calculated on the basis of the change in VC turned out to be the same (maintained at around 0.8) and thus, the planned sample size was not altered. As the Low-dose group was placed to assess benefit-risk profiles of pirfenidone treatment at a tapered dose, the sample size of the Low-dose group was obtained by halving the sample size of the High-dose and Placebo groups. Multiplicity problems were not taken into account because the main analysis was the comparison between the High-dose and Placebo groups.

Analyses of the change in VC and the lowest $SpO_2$ from baseline were performed with the analysis of covariance (ANCOVA) using the respective baseline measurements as covariates. Analyses of the change in other PFTs and the serum levels of the markers of interstitial pneumonias were performed with the least significant difference method based on one-way analysis of variance (ANOVA). The principle of the last observation carried forward (LOCF) was adopted to impute missing values, if patient data were available for at least 4 weeks after the baseline. In order to avoid the bias with the handling of missing values, mixed model approach using available repeated measures of changes in VC was performed as a sensitivity analysis. The cumulative PFS rates were estimated with Kaplan-Meier method and compared with the log-rank test. Incidences were compared with Fisher's exact test.

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

## RESULTS

### Patients enrolled

Between July 2004 and August 2005, 325 patients were screened at 73 centers in Japan, and 275 patients were randomized to one of the three groups: the High-dose, Low-dose and Placebo groups. Of the 275 patients, 267 (108, 55 and 104 patients in the High-dose, Low-dose and Placebo groups, respectively) were deemed eligible for the full analysis set (FAS). Eight patients were excluded due to having no post-baseline data (Fig. 1). The first patient was entered this trial on July 13$^{th}$, 2004, and the last patient was entered on August 30$^{th}$, 2006.

No significant differences were seen in the distribution of the demographic and baseline characteristics among the three groups, except for smoking history (Table 1). A post analysis did not reveal a significant effect of smoking history on the change of VC. Based on the data of their PFTs, patients had been assumed to have relatively mild functional impairment. Two hundred forty-six patients (92 %) had not received prior treatment for IPF including corticosteroids. Eighty-six patients (40, 15 and 31 patients in the High-dose, Low-dose and Placebo groups, respectively) discontinued the study medication for various reasons (Table 2). The main reasons were progression of disease in the Placebo group, and the occurrence of adverse events in both of the pirfenidone-treatment groups. Kaplan-Meier plot of the time to discontinuation for the three groups is shown in Figure E1 (online supplement). The distributions of the time were compared in pairs among the three groups with log-rank test, but no significant differences were seen. Eleven patients (4.1%) died during the study: three, four, and four in the High-dose, Low-dose, and Placebo groups, respectively.

### Effects on primary endpoints

The adjusted means of the changes in VC based on the ANCOVA were -0.09 liter and -0.16 liter in the High-dose and Placebo groups, respectively, with the

difference of 0.07 liter being significant ($p$=0.0416). In addition, the adjusted mean change in the Low-dose group was -0.08 liter and the significant difference was also seen between the Low-dose and Placebo groups ($p$=0.0394) (Fig. 2). The crude means (at baseline and Week 52) and the changes, the adjusted means, mean changes from ANCOVA, and the P-values are summarized in Table 3. The significant difference was not seen between the high dose and low dose groups. The serial changes in vital capacity over the 52-week period are illustrated in Figure 3.

**Effects on secondary and tertiary endpoints**

The secondary endpoints were PFS time and the change in the lowest $SpO_2$ during 6MET. The distribution of PFS time was compared between the High-dose and Placebo groups with the log rank test, and a significant difference was found ($p$=0.0280) (Fig. 4). In addition, a marginally significant difference was found in the distribution between the Low-dose and Placebo groups as well ($p$=0.0655). No statistically significant difference was detected in the mean changes of the lowest $SpO_2$ among the three groups (Table 4). The incidence of acute exacerbation during the study or within 28 days after the termination of the study, was six (5.6%), three (5.5%), and five (4.8%) in the High-dose, Low-dose and Placebo groups, respectively. No significant differences were seen among the three groups. Although between the Low-dose and Placebo groups the differences of mean changes in TLC and those in DLco were statistically significant ($p$=0.0408, $p$=0.0768, respectively) at Week 52, there were no significant differences in the changes of other PFTs or serum markers among the three groups (Table E1; online supplement).

**Compliance and safety**

Significant adverse events reported with the frequency of 5% or more during the study ($p$<0.05) are listed in Table 5. Photosensitivity, anorexia, dizziness and elevated gamma glutamyl-transpeptidase (γ-GTP) were significantly more common in

the High-dose group than in the Placebo group, and photosensitivity, asteatotic eczema, abdominal discomfort and decrease in white blood cell (WBC) were significantly more common in the Low-dose group than in Placebo group. On the other hand, respiratory tract infection, such as nasopharyngitis and upper respiratory tract inflammation, was significantly less common in the High-dose group than the Placebo group.

The adverse events leading to discontinuation of the study are listed in Table 2. Twenty (18.3%) patients in the High-dose group and 11 (20%) in the Low-dose group discontinued the study treatment, with no statistical difference compared to 14 (13.1%) patients in the Placebo group. Most of the adverse events disappeared with a decrease of the dose or temporary withholding of the medication. Therefore, treatment with pirfenidone was generally well tolerated in patients with IPF.

Photosensitivity was the major adverse event observed in 51% of the patients in the High-dose group and 52% in Low-dose group. Approximately 70% and 80% of the patients who developed photosensitivity were mild in severity in the High-dose and the Low-dose group, respectively, and the rest was moderate. Although there were no significant differences in the incidence between the High-dose and Low-dose groups, the percentage of mild photosensitivity was higher in the Low-dose group. The assessment of the degree of the severity was subjective based on patient's symptoms and the site investigator's judgment. Only three patients (approximately 3%) discontinued the study due to photosensitivity.

## DISCUSSION

During the last decade, several clinical trials for IPF have been conducted worldwide to determine an effective treatment regimen for IPF, but the results have been negative and disappointing. Thus, an effective treatment regimen compared to placebo controls, is yet to be determined [5, 6, 21, 28]. In this trial, both High- and Low-dose pirfenidone groups improved VC and the distribution of PFS was better than the placebo group (Fig. 2, Table 3, Fig. 4). Recent studies have confirmed that a fall in vital or forced vital capacity of 10% or more from the baseline over a period of six to 12 months is the most important predictor of mortality in patients with IPF [22-24, 26]. Therefore, disease progression, defined as time to death and/or 10% decline in absolute changes in measured VC, is acknowledged as an appropriate surrogate marker for survival [6, 23] , that is also appropriate regarding lesser changes in FVC reported recently [29]. Considering that over 90% of patients had not received any treatment prior to randomization, our findings provide first evidence that a treatment intervention with a drug improves PFS time in patients with IPF.

No significant differences were found with respect to the changes in the lowest $SpO_2$ amongst the groups in our study (Table 4). While the exact reasons for this apparent negative observations are unknown, the following facts may explain our observations as far as the discrepancy in findings between the previous study [15] and the present one; 1) the 6MET performed in this and the previous study is not a validated test, and 2) the final change in the lowest $SpO_2$ could not be accurately evaluated due to approximately 20% of the patients who could not complete the 6MET during follow up, because their lowest $SpO_2$ had reached 82% (data not shown). Reproducibility of the exercise studies with 6 minute walk test (6MWT) and modified versions of the 6 minute walk/exercise test are confounding factors that need to be clarified in future studies before embarking on using exercise studies such as 6MET/6 MWT [6, 28].

The previous phase II trial in Japan was terminated early because of the incidence of acute exacerbations of IPF [15]. However, in the present trial, no differences were found in the frequency of acute exacerbation among the three groups. While the incidence of acute exacerbation in the placebo group was 14.3% over 9 months in the previous study, this was observed in only 4.8% over 52 weeks in the current study, and thus, the previous observation was not confirmed in the present study. The reasons for this discrepancy are unclear. In then present study, acute exacerbation occurred in only 5% of the patients with relatively mild pulmonary function impairment during one-year. The true incidence and prevalence of the acute exacerbation of IPF is unknown; the frequencies of acute exacerbation have been reported to differ among studies, which are largely retrospective [30]. Nevertheless, our observations regarding acute exacerbation warrant further studies to carefully assess the problem in a well defined, larger study with longer follow data.

The post hoc analysis based on respiratory function categories was carried out in this study to compare the results from our previous phase II study [15]. The improvement ratings of each respiratory function were defined by ATS criteria. There was no significant difference between High-dose group and placebo group (Online supplement, Fig. E2-1). The reasons for these differences between the two studies are unknown. However, the difference between High-dose group and placebo group was significant ($p=0.0109$), when the categorized analysis of the changes in VC was based on the rating of a lesser magnitude [29] (Online supplement, Fig. E2-2).

The adverse event that occurred significantly more often among patients in both the High- and Low-dose pirfenidone groups was photosensitivity, a well known side effect associated with pirfenidone and documented in previous studies [7, 15]. Anorexia and elevated γ-GTP were significantly more common in the High-dose group than in the Placebo group, which are also similar results observed in our phase II study

[15]. Although the overall incidence of adverse events in the pirfenidone treatment groups was relatively high, no significant differences were detected in the frequency of the patients who discontinued the study between the pirfenidone treatment groups and the placebo group. This may be in part that the patients were well informed regarding the side effect of rashes. Despite the manifestation of the anticipated skin rash, pirfenidone was generally well tolerated in IPF patients.

Potential limitations with this study include the change in decision of the primary endpoint during the study. Despite the evolved knowledge that the change in VC at 12 months correlated well with survival [22-24, 26], we had initially chosen the lowest $SpO_2$ during 6MET as the primary endpoint for this study as we were encouraged with the novel observations made in our previous study [15]. Change in VC was initially intended to be a secondary endpoint. Acknowledging that the 6MET employed in our Phase II study needed to be validated, a validation study was conducted to evaluate the lowest $SpO_2$ during 6MET prior to the initiation of the Phase III study (research supported by health and labor sciences research grants). VC and PFS were selected as key secondary endpoints to support the primary endpoint and the power of test for VC and PFS was based on the sample size calculated from the lowest $SpO_2$ in the first version of the protocol itself. However, significant difficulties were confronted during the validation study for the 6MET and several patients discontinued participating in that study. Because of the concerns of assessing the efficacy of pirfenidone based on the lowest $SpO_2$ measured every 12 weeks compared to the VC that was measured every four weeks and of the potential of unexpectedly large fluctuations between each point in the lowest $SpO_2$ along with the problems of reliability/reproducibility of the $SpO_2$ measurement during exertion such as walking [27] and acknowledging that the change in VC or FVC was increasingly being used as the primary endpoint in other clinical studies [5, 21], the primary endpoint was changed

from the lowest $SpO_2$ during 6MET to VC during the study period. While this change in the primary endpoint may be considered as a major limitation for this study, it should be noted that the decision to change the endpoint was prior to code-breaking according to the recommendation of the independent DSMB and the sample size was unaffected.

We acknowledge the limitation associated with the treating of missing values. It is generally known that results of analyses may have potential bias when missing values were imputed with some method, and that there is no perfect imputation method which performs best in all the circumstances. In this study, we adopted LOCF, since LOCF was adopted in the previous study. We were under the impression that LOCF may not tip the balance in favor of either of the treatment groups in case no substantial difference in the rate of drop-outs was seen. Mixed model approach using repeated measures of changes in VC without LOCF imputation as a sensitivity analysis also showed significant or marginally significant treatment effects and supported the LOCF analysis. Figure 3 shows the transitional plot of the changes in VC over 52 weeks. Both the 'LOCF imputed means' and 'crude means' of the changes within 16 weeks, suggested favourable effect of pirfenidone, and not affected by drop-outs.

Other potential limitations with our study include; 1) a selection bias as patients enrolled in this study needed to be able to perform the 6MET at baseline in accordance to the protocol; the results in this selected group of patients with mild functional impairment may not therefore be applicable to all patients with IPF with varying degrees of pulmonary symptoms and functional impairment. 2) The lack of central pathology review is another potential limitation. While we acknowledge these limitations, it must be noted that the patient population enrolled in this study included all consecutive, eligible and consenting patients from the general patient population with IPF with mild functional impairment.

In conclusion, the results of the phase III clinical trial demonstrate that

pirfenidone, a novel antifibrotic agent, preserves VC and improves PFS better than placebo in Japanese patients with IPF with mild functional impairment without serious adverse events. Future studies may confirm our findings further.

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**Members of Pirfenidone Clinical Study Group;**

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Kyusyu National Hospital)

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**Table 1. Baseline Characteristics of the Study Population (FAS)**

| Characteristic | High-dose (n = 108) | Low-dose (n = 55) | Placebo (n = 104) | p-value[#] |
|---|---|---|---|---|
| Sex | | | | |
| Male | 85 (78.7) | 47 (85.5) | 81 (77.9) | 0.53 |
| Female | 23 (21.3) | 8 (14.5) | 23 (22.1) | |
| Age (yr) | 65.4±6.2 | 63.9±7.5 | 64.7±7.3 | 0.44 |
| Smoking history | | | | |
| Smokers | 5 (4.6) | 10 (18.2) | 13 (12.5) | 0.07* |
| Ex-smokers | 81 (75.0) | 33 (60.0) | 70 (67.3) | |
| Never smokers | 22 (20.4) | 12 (21.8) | 21 (20.2) | |
| Yrs since first diagnosis | | | | |
| < 1 yr | 38 (35.2) | 20 (36.4) | 41 (39.4) | 0.86 |
| 1-3 yr | 29 (26.9) | 13 (23.6) | 25 (24.0) | |
| > 3 yr | 41 (38.0) | 22 (40.0) | 38 (36.5) | |
| Prior treatment (steroids) - | 99 (91.7) | 49 (89.1) | 98 (94.2) | 0.49 |
| + | 9 (8.3) | 6 (10.9) | 6 (5.8) | |
| Current steroid use | 8 (7.4) | 6 (10.9) | 5 (4.8) | - |
| Surgical lung biopsy | 26 (24.1) | 16 (29.1) | 28 (26.9) | 0.78 |
| VC (mL) | 2400.8±638.4 | 2437.8±684.8 | 2472.3±698.9 | 0.74 |
| VC % pred | 77.3±16.8 | 76.2±18.7 | 79.1±17.4 | 0.57 |
| TLC % pred | 73.2±16.5 | 72.4±15.6 | 75.2±15.7 | 0.50 |
| DLco % pred | 52.1±16.8 | 53.6±19.1 | 55.2±18.2 | 0.44 |
| $PaO_2$ at rest mmHg | 79.8±10.2 | 81.6±8.4 | 81.0±9.5 | 0.48 |
| $AaDO_2$ mmHg | 18.4±11.3 | 16.9±9.6 | 17.4±9.7 | 0.64 |
| Lowest $SpO_2$ % | 89.0±2.3 | 88.8±2.4 | 89.0±2.0 | 0.86 |
| Presence of desaturation below 88% on walk test | 34 (31.5) | 19 (34.5) | 24 (23.1) | - |

Data are presented as n, n(%) or mean ± SD. High-dose: High-dose group of pirfenidone; Low-dose: Low-dose group of pirfenidone; Placebo: Placebo group; VC: vital capacity; TLC: total lung capacity; DLco: diffusion capacity of the lung for carbon monoxide; $PaO_2$: partial pressure of arterial oxygen; $AaDO_2$: alveolar-arterial oxygen tension difference; $SpO_2$: oxygen saturation, #: using Fisher's exact test, Kruskal-Wallis test and ANCOVA in accordance with nominal and binary, ordinal and continuous data, respectively. *: $p<0.15$. VC, TLC, DLco, $PaO_2$ and $AaDO_2$ were measured for 106 subjects in the High-dose pirfenidone group, and TLC and DLco for 103 subjects in the Placebo group.

| Table 2. Reason for Discontinuation of the Study (FAS) | | | |
|---|---|---|---|
| Reasons for Discontinuation | High-dose (n = 108) | Low-dose (n = 55) | Placebo (n = 104) |
| Total | 40 (37.0) | 15 (27.3) | 31 (29.8) |
| Progression of disease | 8 (7.4) | 0 (0.0) | 15 (14.4) |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 10% decline in VC | 5 (4.6) | 0 (0.0) | 11 (10.6) |
| Worsening of respiratory symptoms | 3 (2.8) | 0 (0.0) | 4 (3.7) |
| Acute exacerbation | 4 (3.7) | 2 (3.6) | 4 (3.8) |
| Adverse events[#] | 15 (13.9) | 9 (16.4) | 7 (6.7) |
| Photosensitivity | 3 (2.8) | 2 (3.6) | 0 (0.0) |
| Lung carcinoma | 2 (1.8) | 1 (1.8) | 1 (0.9) |
| Fever | 2 (1.8) | 0 (0.0) | 0 (0.0) |
| Respiratory failure[†] | 2 (1.8) | 0 (0.0) | 0 (0.0) |
| Rash | 1 (0.9) | 1 (1.8) | 0 (0.0) |
| AST and/or ALT increase | 1 (0.9) | 1 (1.8) | 0 (0.0) |
| Gastric ulcer | 1 (0.9) | 0 (0.0) | 0 (0.0) |
| Anorexia | 1 (0.9) | 0 (0.0) | 0 (0.0) |
| Muscle pain | 1 (0.9) | 0 (0.0) | 0 (0.0) |
| Dysgeusia | 1 (0.9) | 0 (0.0) | 0 (0.0) |
| Loss of consciousness | 1 (0.9) | 0 (0.0) | 0 (0.0) |
| Respiratory tract infection | 0 (0.0) | 2 (3.6) | 0 (0.0) |
| Fatigue, drowsiness | 0 (0.0) | 1 (1.8) | 0 (0.0) |
| Rheumatoid arthritis | 0 (0.0) | 1 (1.8) | 0 (0.0) |
| Electrocardiogram abnormal | 0 (0.0) | 0 (0.0) | 2 (1.9) |
| Nausea | 0 (0.0) | 0 (0.0) | 1 (0.9) |
| Lung neoplasm | 0 (0.0) | 0 (0.0) | 1 (0.9) |
| MPO-ANCA increase | 0 (0.0) | 0 (0.0) | 1 (0.9) |
| Cerebral thrombosis | 0 (0.0) | 0 (0.0) | 1 (0.9) |
| Suicide | 0 (0.0) | 0 (0.0) | 1 (0.9) |
| Upper respiratory tract infection | 0 (0.0) | 0 (0.0) | 1 (0.9) |
| Pneumothorax | 0 (0.0) | 0 (0.0) | 1 (0.9) |
| Consent withdrawn | 12 (11.1) | 2 (3.6) | 4 (3.8) |
| Other | 1 (0.9) | 2 (3.6) | 1 (1.0) |

Data are presented as n or n(%). [#]: Other than acute exacerbation. High-dose: High-dose pirfenidone group; Low-dose: Low-dose pirfenidone group; Placebo: Placebo group.

| Table 3. Comparison of Changes in VC | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Crude mean± SD | | | | Comparison of adjusted means based on the ANCOVA[#] | | | |
| | Baseline (L) | N | 52 weeks (L) | N | Subject N | Adjusted mean ± SE | Difference from placebo group (L) | p-value |
| High-dose | 2.40 ± 0.64 | 106 | 2.36 ± 0.73 | 67 | 104 | -0.09 ± 0.02 | 0.07 ± 0.03 | 0.0416 |
| Low-dose | 2.44 ± 0.68 | 55 | 2.34 ± 0.71 | 38 | 54 | -0.08 ± 0.03 | 0.09 ± 0.04 | 0.0394 |
| Placebo | 2.47 ± 0.70 | 104 | 2.42 ± 0.75 | 72 | 103 | -0.16 ± 0.02 | - | - |

Data are presented as mean ± SD (or SE). [#]: Comparison of adjusted means based on the ANCOVA (negative and positive of the changes represent deterioration and improvement from baseline, respectively). Covariates: Baseline VC. High-dose: High-dose pirfenidone group; Low-dose: Low-dose pirfenidone group; Placebo: Placebo group.

| **Table 4. Comparison of Changes in the lowest $SpO_2$** | | | | |
|---|---|---|---|---|
| Group | Subject ( N ) | Adjusted mean ± SE | Difference from placebo group (%) | p-value # comparison with Placebo |
| High-dose | 99 | - 1.70 ± 0.35 | - 0.17 ± 0.50 | 0.7393 |
| Low-dose | 53 | - 0.84 ± 0.48 | 0.69 ± 0.59 | 0.2485 |
| Placebo | 100 | - 1.53 ± 0.35 | - | - |

#: Comparison of adjusted means based on the ANCOVA

**Table 5. Significant Adverse Events**

| Adverse event | High-dose (N=109) | Low-dose (N=55) | Placebo (N=107) | p-value[#] | | |
|---|---|---|---|---|---|---|
| | | | | High-dose vs Placebo | Low-dose vs Placebo | High-dose vs Low-dose |
| Any adverse event | 109 (100.0) | 54 (98.2) | 106 (99.1) | 0.45 | 1.00 | 0.34 |
| Photosensitivity | 56 (51.4) | 29 (52.7) | 24 (22.4) | <0.01 | <0.01 | 1.00 |
| Eczema asteatotic | 0 (0.0) | 3 (5.5) | 0 (0.0) | - | 0.04 | 0.04 |
| Anorexia | 18 (16.5) | 6 (10.9) | 3 (2.8) | <0.01 | 0.06 | 0.48 |
| Abdominal discomfort | 3 (2.8) | 4 (7.3) | 0 (0.0) | 0.25 | 0.01 | 0.23 |
| Dizziness | 8 (7.3) | 0 (0.0) | 1 (0.9) | 0.04 | 1.00 | 0.05 |
| Nasopharyngitis | 54 (49.5) | 30 (54.5) | 70 (65.4) | 0.02 | 0.23 | 0.62 |
| Upper respiratory tract infection | 1 (0.9) | 3 (5.5) | 9 (8.4) | <0.01 | 0.75 | 0.11 |
| γ-GTP elevation | 25 (22.9) | 12 (21.8) | 10 (9.3) | <0.01 | 0.05 | 1.00 |
| WBC decrease | 4 (3.7) | 3 (5.5) | 0 (0.0) | 0.12 | 0.04 | 0.69 |

Data are presented as n or n(%). Significant adverse events: adverse events which were observed with an incidence of >5% during the study period and for which a significant difference was detected between the placebo group and each of the pirfenidone treatment groups, High-dose or Low-dose ($p<0.05$). High-dose: High-dose pirfenidone group; Low-dose: Low-dose pirfenidone group; Placebo: Placebo group; γ-GTP: gamma-glutamyltranspeptidase. [#]: using Fisher's exact test.

## FIGURE LEGENDS

**Figure 1. Disposition of patients**

325 patients were screened at 73 centers in Japan, and 275 patients were randomized to one of the three groups: High-dose (1800 mg/day of pirfenidone), Low-dose (1200 mg/day) and Placebo groups. Of the 275 patients, 267 (108, 55 and 104 patients in the High-dose, Low-dose and Placebo groups, respectively) were deemed eligible for the full analysis set (FAS). Eight patients were excluded due to having no post-baseline efficacy data, in which four subjects who had not been treated and four subjects with no efficacy data after 4 weeks. Disease progression includes 10% decline in VC and worsening of respiratory symptoms.

**Figure 1**

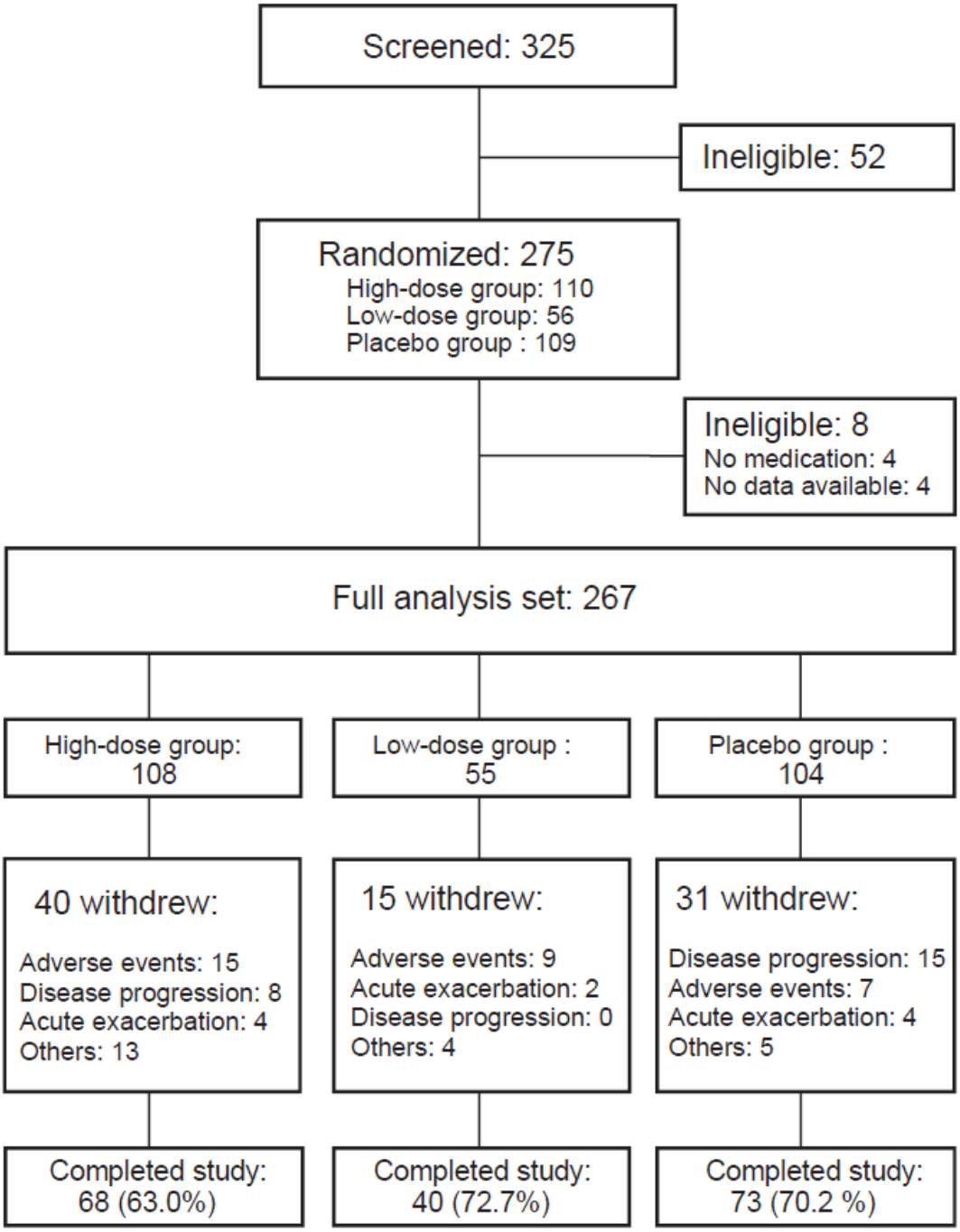

Screened: 325
Ineligible: 52
Randomized: 275
High-dose group: 110
Low-dose group: 56
Placebo group : 109
Ineligible: 8
No medication: 4
No data available: 4
Full analysis set: 267
High-dose group: 108
Low-dose group : 55
Placebo group : 104
40 withdrew:
Adverse events: 15
Disease progression: 8
Acute exacerbation: 4
Others: 13
15 withdrew:
Adverse events: 9
Acute exacerbation: 2
Disease progression: 0
Others: 4
31 withdrew:
Disease progression: 15
Adverse events: 7
Acute exacerbation: 4
Others: 5
Completed study: 68 (63.0%)
Completed study: 40 (72.7%)
Completed study: 73 (70.2 %)

**Figure 2. Effects of Pirfenidone on VC at Week 52**

Data are presented as mean ± SE. *: p<0.1, comparison of adjusted means based on the ANCOVA (negative and positive of the changes represent deterioration and improvement from baseline, respectively). LOCF method was used for dropouts in each group. High-dose: High-dose pirfenidone group; Low-dose: Low-dose pirfenidone group; Placebo: Placebo group.

**Figure 2**

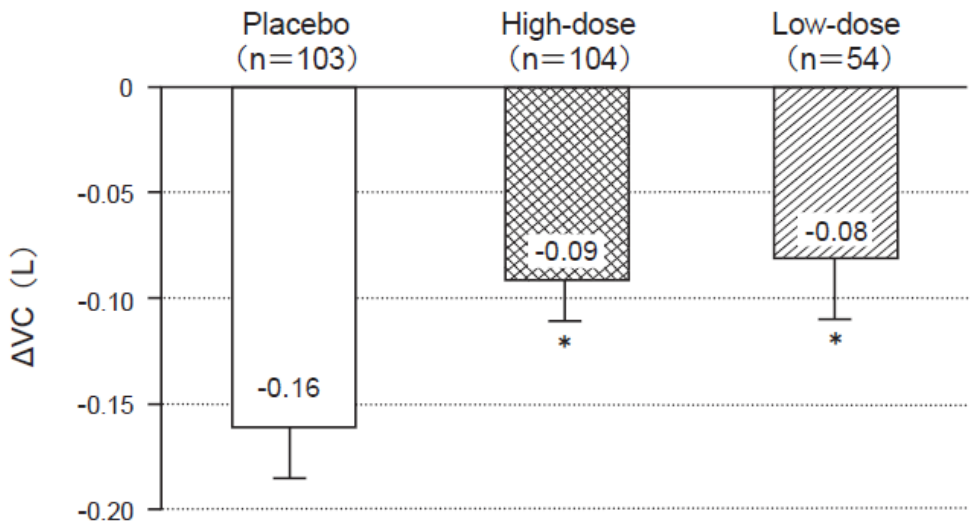
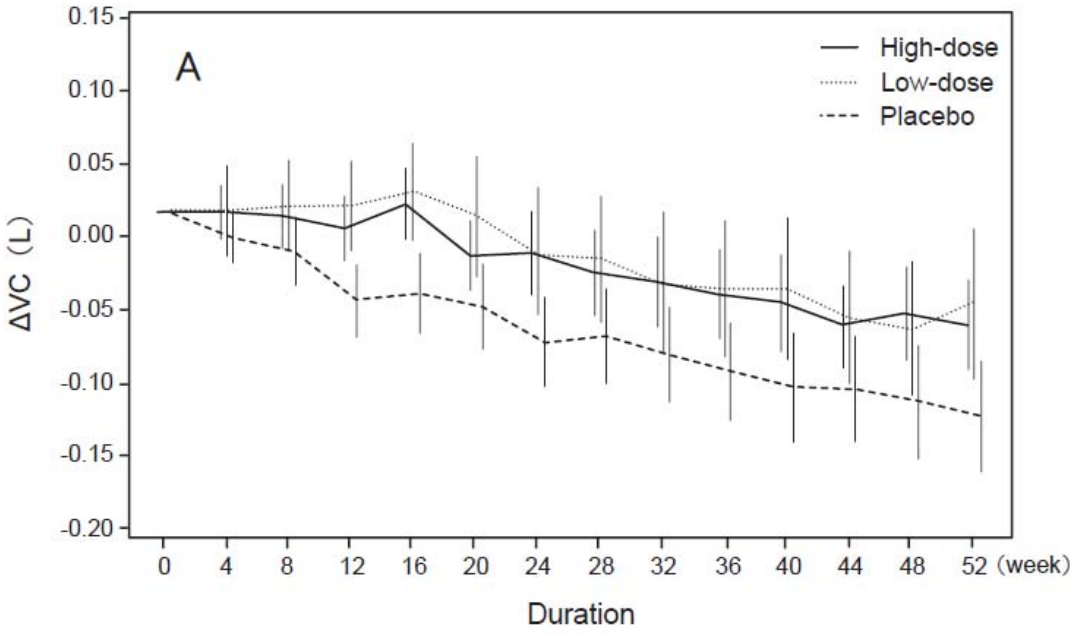
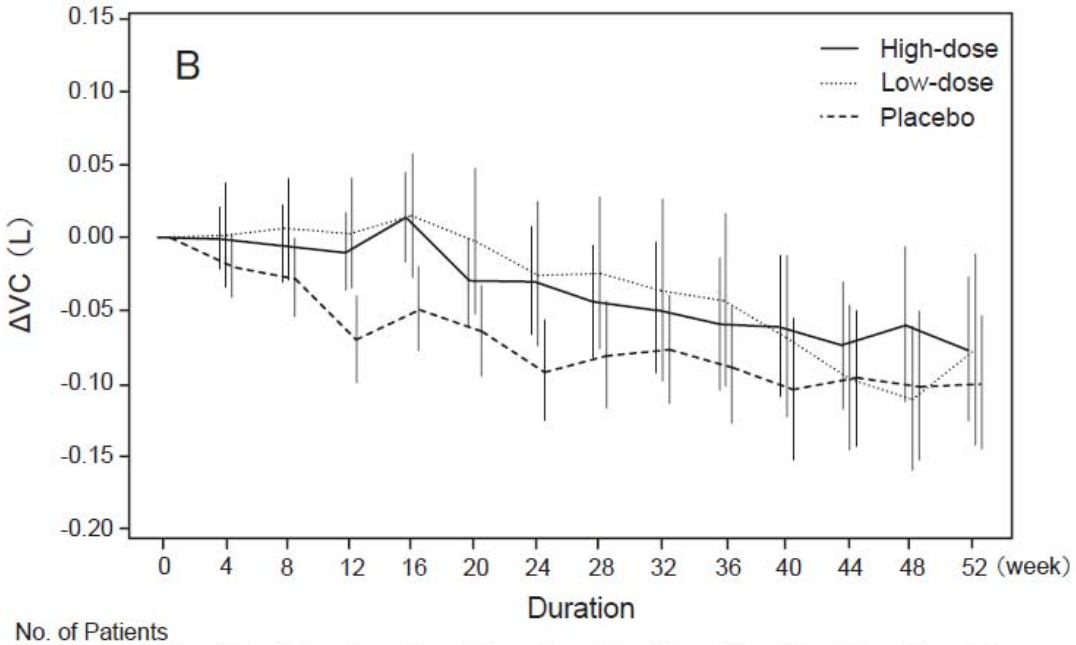


**Figure 3. The serial changes in VC every 4 weeks over 52 weeks**

A; The transitional plots of 'LOCF imputed means' and, B; 'crude means' of the changes in VC, respectively. High-dose: High-dose pirfenidone group; Low-dose: Low-dose pirfenidone group; Placebo: Placebo group.

**Figure 3**




No. of Patients

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| High-dose | 106 | 103 | 102 | 97 | 93 | 91 | 90 | 86 | 78 | 76 | 75 | 67 | 65 | 66 |
| Low-dose | 55 | 54 | 54 | 52 | 49 | 50 | 48 | 47 | 44 | 44 | 42 | 41 | 40 | 38 |
| Placebo | 104 | 103 | 103 | 100 | 98 | 95 | 95 | 93 | 84 | 82 | 79 | 76 | 74 | 72 |

**Figure 4. Kaplan-Meier plot of PFS time among IPF patients groups**

Symbols on the curve represent the censored points where patients discontinued the study treatment due to causes other than progression of the disease. Kaplan-Meier curves were compared with Log-rank test: p=0.0280 between the High-dose group and Placebo group; 0.0655 between the Low-dose group and Placebo group; 0.9106 between the High-dose group and Low-dose group.

**Figure 4**