Long-term effect of pulmonary rehabilitation in idiopathic pulmonary fibrosis: a randomised controlled trial


ABSTRACT

Background Idiopathic pulmonary fibrosis (IPF) is characterised by worsening dyspnoea and exercise intolerance.

Research question Does a long-term pulmonary rehabilitation improve exercise tolerance in patients with IPF treated with standard antifibrotic drugs, which are expected to reduce disease progression?

Methods This open-label randomised controlled trial was performed at 19 institutions. Stable patients receiving nintedanib were randomised into pulmonary rehabilitation and control groups (1:1). The pulmonary rehabilitation group underwent initial rehabilitation which included twice-weekly sessions of monitored exercise training for 12 weeks, followed by an at-home rehabilitation programme for 40 weeks. The control group received usual care only, without pulmonary rehabilitation. Both groups continued to receive nintedanib. The primary and secondary outcomes were change in 6 min walking distance (6MWD) and change in endurance time (using cycle ergometry) at week 52.

Results Eighty-eight patients were randomised into pulmonary rehabilitation (n=45) and control (n=43) groups. Changes in 6MWD were −33 m (95% CI −65 to −1) and −53 m (95% CI −86 to −21) in the pulmonary rehabilitation and control groups, respectively, with no statistically significant difference (mean difference, 21 m (95% CI −25 to 66), p=0.38). Changes in endurance time were significantly better in the pulmonary rehabilitation (64 s, 95% CI −42.3 to 171) than in the control (−123 s (95% CI −232 to −13)) group (mean difference, 187 s (95% CI 34 to 153), p=0.019).

Interpretation Although pulmonary rehabilitation in patients taking nintedanib did not improve 6MWD in the long term, it led to prolonged improvement in endurance time.

Trial registration number UMIN000026376.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an intractable disease characterised by chronic, irreversible progression of fibrosis. The natural history of IPF includes worsening of pulmonary function, dyspnoea on exertion, exercise intolerance, reduced physical activity and quality of life impairment. Patients with IPF have needs for prolonged...
HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The combination of nintedanib and pulmonary rehabilitation in patients with IPF resulted no difference in 6MWD compared with usual care with nintedanib, but a greater improvement in endurance time. Thus, pulmonary rehabilitation with nintedanib may be effective in improving long-term exercise capacity, although further studies with strategies such as the inclusion of a sophisticated long-term maintenance programme are needed before it can be recognised as a robust care protocol for patients with IPF.

improvement in these impairments, but optimal management for meeting those needs has not been established.

Pulmonary rehabilitation is expected to be effective in improving dyspnoea and exercise tolerance in patients with chronic respiratory disorders, and several studies have reported the benefits of pulmonary rehabilitation in interstitial lung disease, including the effects of pulmonary rehabilitation on IPF. A majority of the previous studies showed short-term benefits of pulmonary rehabilitation on IPF. A few studies evaluated the long-term effects at 6 months or longer; but failed to demonstrate any long-term positive effects of pulmonary rehabilitation on exercise tolerance. The findings, therefore, suggest that conventional pulmonary rehabilitation alone may not lead to prolonged improvement in exercise tolerance, which could be attributed to the relatively rapid progression of disease in IPF.

Past studies have demonstrated that the benefits of a few months of pulmonary rehabilitation wane in patients with IPF after 6 months; therefore, we believe it is necessary to develop an effective way to maintain long-term effectiveness. Programmed maintenance rehabilitation in addition to a regular rehabilitation programme would seem to be a promising approach, but there are no studies of outpatient induction rehabilitation, followed by maintenance rehabilitation.

Antifibrotic agents are currently a conditional recommended treatment for IPF to slow disease progression and suppress the decline of exercise capacity, and to prevent acute exacerbation. They are also expected to sustain the effects of pulmonary rehabilitation. Therefore, in the current antifibrotic era, pulmonary rehabilitation may be expected to take place concurrently with the administration of antifibrotic agents, but in the three previous studies that evaluated the effect of long-term pulmonary rehabilitation for IPF, only a small percentage (0.9–9.4%) of patients received antifibrotic agents.

In this study, we hypothesised that a long-term rehabilitation programme (induction rehabilitation followed by maintenance rehabilitation) would have a long-term effect on maintaining or slowing the decline in exercise capacity in patients with IPF receiving a standard drug therapy of nintedanib.

METHODS

Study design and participants

The FITNESS (Long-term effect of pulmonary rehabilitation under nintedanib in idiopathic pulmonary fibrosis) study was a multicentre, randomised, prospective, parallel-group, unblinded, controlled trial performed at 19 institutions in Japan (online supplemental e-Table 1). The pulmonary rehabilitation group underwent initial rehabilitation that included twice-weekly sessions of monitored exercise training for 12 weeks, followed by an at-home rehabilitation programme for 40 weeks. The control group received usual care only, without pulmonary rehabilitation. Both groups continued to receive nintedanib. The purpose, design and methods of the study, which were previously reported and the final protocol, are available in online supplemental appendix.

The main inclusion criteria were as follows: (1) age between 40 and 79 years at the time of consent, (2) diagnosis of IPF based on the 2011 guideline criteria, (3) previous 6 min walking distance (6MWD) of 200 m or more and less than 600 m, (4) dyspnoea on exertion (modified Medical Research Council (mMRC) grade scale 1–3), (5) stable disease without infection or acute exacerbation within 3 months prior to enrolment and (6) receiving nintedanib (150 mg or 100 mg two times per day) for at least for 4 weeks and able to receive the drug for more than 12 months after registration.

Randomisation

Eligible patients were randomised into the pulmonary rehabilitation and control groups in a 1:1 ratio with a minimisation method using a web-based system. The dynamic randomisation factors were baseline 6MWD during the screening period (≥350 m or <350 m), institutions and forced vital capacity (FVC) at registration (the cut-off value was calculated as 70% of the predictive value). Study group allocation was performed via an electronic data capture system using computer-generated random numbers. Study physicians and patients were aware of the allocated study group.

Pulmonary rehabilitation programme

In this study, physical function assessment and the pulmonary rehabilitation programme were performed by a cardiopulmonary physiotherapist at each institution. To equalise the evaluation methods for exercise tolerance and the pulmonary rehabilitation programmes, a detailed protocol was developed prior to the study. In addition, physical therapists in each participating institution were required to participate in joint practical training.

The detailed rehabilitation programme is described in a previous report and will be briefly introduced. During the first 12 weeks after the start of the pulmonary rehabilitation programme, induction pulmonary rehabilitation was performed during two outpatient visits per week (24 sessions) under the supervision of a cardiopulmonary physiotherapist. In addition to the outpatient visits, participants were instructed to perform self-rehabilitation at home at least twice a week in the induction pulmonary rehabilitation phase (online supplemental appendix, page 25). The initial pulmonary rehabilitation included 30 min of endurance training using a cycle ergometer and walking, and resistance training. Endurance training intensity in cycling targeted 80% of the peak work rate, and the initial intensity for cycling was 80% of the walking speed achieved on the baseline 6 min walk test. Depending on the improvement in maximum exercise tolerance, resistance training of the upper and lower limbs was performed using free weights or the patient’s own body weight, with gradually increasing load. A home exercise programme was also prescribed during the pulmonary rehabilitation programme; squatting and standing calf raises were used for resistance training. The initial pulmonary rehabilitation programme was followed by the 40-week maintenance programme, consisting of self-training at home and outpatient pulmonary rehabilitation supervised by a cardiopulmonary physiotherapist (more than once every 4 weeks).
were required to record the status of self-training and the daily number of steps in a diary.

**Study outcomes**

**Primary outcome**

The primary outcome was the result of a comparison between the two groups in terms of changes in 6MWD between baseline and week 52.

**Secondary outcomes**

The main secondary outcome was the result of comparison of changes in endurace time between baseline and week 52 in the two groups, as measured using cycle ergometry\(^\text{21}\) (see online supplemental appendix).

Other outcomes were the results of a comparison of changes in parameters between baseline and week 52 in the two groups. These parameters included the total score on the St. George’s Respiratory Questionnaire (SGRQ),\(^\text{22}\) the rate of changes (\%) from baseline evaluation of 6MWD, number of daily steps, each SGRQ component score, Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT),\(^\text{23–25}\) dyspnoea (Transitional Dyspnoea Index (TDI),\(^\text{26}\) Dyspnoea-12),\(^\text{27}\) Hospital Anxiety and Depression Scale (HADS),\(^\text{28}\) changes from baseline to end of pulmonary rehabilitation programme until the time of evaluation (week 52) were compared. Changes in 6MWD between baseline and week 52 were also compared between the high and low pulmonary rehabilitation compliance (\(\geq 70\%\)) and with the long-term pulmonary rehabilitation programme until the time of evaluation (week 52) were compared. Changes in 6MWD between baseline and week 52 were also compared between the high and low pulmonary rehabilitation compliance (\(\geq 70\%\) and <70\%, respectively) subgroups. One review reported rates of adherence to home exercise programmes, with mean percentage rate of adherence across studies of 67\%.\(^\text{29}\) We preliminarily defined the ‘good compliance group’ as those who performed the pulmonary rehabilitation at least five times a week (approximately 70\%).

**Statistical analysis**

**Sample size**

There are limited data from previous studies estimating the magnitude of increase in 6MWD after rehabilitation in combination with nintedanib treatment. For patients treated with nintedanib, the decreasing gradient in 6MWD was considered low, although the actual value was unknown. As the maintenance pulmonary rehabilitation programme could facilitate long-term maintenance of the previously reported effects of short-term pulmonary rehabilitation programmes, we hypothesized that the effects of the combination of programmed long-term pulmonary rehabilitation and nintedanib may be equivalent to those of short-term pulmonary rehabilitation. Based on the four previous short-term pulmonary rehabilitation studies for IPF described in the review reported,\(^\text{13}\) the SD of the 6MWD predifference and postdifference was calculated to be 55 m. In this study, the expected value of the difference in the pre/post 6MWD between the nintedanib with and without long-term rehabilitation group was set at 36 m. Based on the above, we calculated that the sample size required to show a significant difference at the primary endpoint with 80% power in a two-tailed test (5% level of significance) was 37 patients in each group, for a total of 74 patients. In anticipation of drop-outs, we set a target of 42 patients per group for a total of 84 patients. As for the main secondary endpoint, based on previous studies,\(^\text{13}\) the difference between prepherehabilitation and postrehabilitation endurance time, as measured using a cycle ergometer, was estimated to be 10 min. For the achieved target sample size of 84 patients, a statistical power of \(\geq 90\%\) (at \(p<0.05\)) was calculated to be sufficient for detecting a statistically significant difference between the treatment groups.\(^\text{30}\) The sample size for this study was similar to that of the previous HOPE IPF study.\(^\text{30}\)

**Outcome analysis**

Efficacy analysis was performed on intention-to-treat basis, using a full analysis set consisting of all randomised patients having undergone baseline evaluation and at least one postbaseline evaluation. Data handling was defined for each outcome, and safety analysis was performed in patients who received nintedanib at least once after registration. Comparisons of changes in 6MWD from baseline were performed between the treatment groups considering \(p<0.05\) (two tailed) as significant, using a mixed-effect model for repeated measures. Least squares mean and 95\% CIs were calculated using a linear mixed-effect model for repeated measures with each treatment group, 6MWD at baseline (randomisation), time of evaluation and the interaction term for each treatment group and time of evaluation as fixed effects. Changes in endurance time from baseline, as measured with a cycle ergometer, were also compared between the two groups using a mixed-effect model for repeated measures. Other secondary outcomes (the number of steps, health status (SGRQ and CAT scores), dyspnoea (TDI and Dyspnoea-12 scores), FVC, DLCO, modified MRC grade and the minimum saturation of percutaneous oxygen after the 6 min walk test) were also evaluated using the same method. For severe cardiac complications, the number of patients with ischaemic heart disease or arrhythmia requiring treatment was calculated and compared between the treatment groups using Fisher’s exact test. Other adverse events were also calculated and compared between the two groups using Fisher’s exact test. In all analyses, a \(p<0.05\) was considered statistically significant. This study was registered with UMIN-CTR (number: UMIN000026376).

**RESULTS**

Ninety-four patients underwent evaluation for eligibility between 30 October 2017 and 23 January 2020. During the screening period, six patients were excluded as they were ineligible, and the remaining 88 patients were allocated into the pulmonary rehabilitation (n=45) and control (n=43) groups (figure 1). The mean age was 70.7 years (SD 3.0). The duration of IFP was 27.7 months (SD 13.1), and the mean duration of nintedanib treatment was 293 days (SD 177); the mean FVC was 2435 mL (SD 400), which was 73.9\% of the predictive value (SD 7.9\%). There was no significant difference in patient characteristics at randomisation between the two groups (table 1).

During the study, there were seven drop-outs in each group; 38 (84\%) and 36 (84\%) patients in the pulmonary rehabilitation and control groups, respectively, completed the evaluation at week 52.
In the pulmonary rehabilitation group, the 6MWD decreased from 447 m at baseline (95% CI 423 to 472) to 415 m at week 52 (95% CI 376 to 455). In the control group, the 6MWD decreased from 459 m at baseline (95% CI 435 to 484) to 406 m at week 52 (95% CI 365 to 446). Changes between baseline and week 52 6MWD (primary outcome) were −33 m (95% CI −65 to −1) in the pulmonary rehabilitation group and −53 m (95% CI −86 to −21) in the control group; there was no statistically significant difference between the two groups (mean difference, 21 m (95% CI −25 to 66), p=0.38). Changes between baseline and week 12 6MWD were 18 m (95% CI 4 to 32) in the pulmonary rehabilitation group and −5 m (95% CI −19 to 9) in the control group (p=0.029). Likewise, changes between baseline and week 26 6MWD in the pulmonary rehabilitation and control groups were 15 m (95% CI −2 to 33) and −16 m (95% CI −34 to −1), respectively (p=0.013) (figure 2).

In the pulmonary rehabilitation group, the endurance time measured using a cycle ergometer increased from 372 s at baseline (95% CI 328 to 557). In the control group, the endurance time measured using a cycle ergometer decreased from 396 s at baseline (95% CI 320 to 455) to 441 s at week 52 (95% CI 325 to 557). Changes between the baseline and week 52 endurance times (main secondary outcome) were significantly better in the pulmonary rehabilitation group (64 s (95% CI −42.3 to 171)) than in the control group (−123 s (95% CI −232 to −13)) (mean difference, 187 s (95% CI −34 to −1), respectively (p=0.013) (figure 2).

As with comparisons of absolute values, comparisons of the percentage of change in 6MWD from baseline showed a significant difference at weeks 12 and 26, but not at week 52. The TDI at all evaluation points was significantly higher in the pulmonary rehabilitation than in the control group (online supplemental figure 1). In the pulmonary rehabilitation group, the FVC changed from 75.0% at baseline (95% CI 70.9% to 79.1%) to 72.0% at week 52 (95% CI 67.1% to 76.9%).

There was no significant difference between the two groups (p=0.37). There was no significant difference between the two groups in terms of SGRQ, CAT, Dyspnoea-12 and HADS scores, number of steps measured by a pedometer, oxygen saturation and FVC at any evaluation point.
After excluding two patients (who did not keep a diary) from the 45 patients in the pulmonary rehabilitation group, there were 21 and 22 patients in the high and low compliance groups, respectively. In these groups, compliance with the pulmonary rehabilitation programme was found to be 93.5% (95% CI 90.2% to 96.8%) and 46.9% (95% CI 42.1% to 51.7%), respectively. Changes between baseline and week 52 6MWD were significantly smaller in the high compliance group (−8 m (95% CI −47 to 31)) than in the low compliance group (−106 m (95% CI −172 to −40)) (p=0.017) (online supplemental e-Figure 2). The incidence of adverse events was equivalent between the two groups (table 3). The incidence of diarrhoea was 74% and 79% in the pulmonary rehabilitation and control groups, respectively; the incidence of diarrhoea of grade 3 or above was 7% in both groups. Acute exacerbation of IPF during the study period was observed in 5 (11%) and 4 (9%) patients, respectively. There were two deaths in each group; the cause of death in all cases was acute exacerbation of IPF.

Nintedanib compliance in the pulmonary rehabilitation and control groups was found to be 94% (95% CI 89.1% to 98.8%) and 96% (95% CI 92.9% to 99.1%), respectively.

**DISCUSSION**

Currently, antifibrotic drugs are the standard therapy for IPF. The FITNESS study was the first randomised controlled trial to evaluate the effects of long-term pulmonary rehabilitation combining induction rehabilitation with subsequent maintenance rehabilitation in patients taking antifibrotic drugs. This is also the largest study to evaluate the effects of pulmonary rehabilitation in 88 patients with IPF alone. The findings showed no significant difference between the two groups in terms of changes in 6MWD between baseline and week 52 (the primary outcome). However, the change in endurance time using cycle ergometry (main secondary outcome), was significantly better in the pulmonary rehabilitation group than in the control group. The mean reduction in FVC at week 52 was 116 mL; this was similar to that of previous studies on the effects of nintedanib.13

Although the intervention in this study did not lead to a significant difference in 6MWD between the two groups, significantly positive effects were observed in terms of endurance time. This could be due to the difference in responsiveness to evaluation. As numerous studies have used 6MWD as the primary outcome measure to evaluate the effects of pulmonary rehabilitation on interstitial lung diseases,3–9 11 12 this study used changes in 6MWD as the primary outcome measure to evaluate the impact of combined therapy in patients with IPF. Endurance time was used as the main secondary outcome measure, because one of our previous studies demonstrated that endurance time was the most sensitive measure of the positive effects of rehabilitation in IPF.25 Recent reports indicate that constant load tests of submaximal exercise performance, similar to those of daily activities, reflect the severity of shortness of breath better than tests of peak exercise performance (such as the 6 min walk test).30 Indeed, some studies have recently used changes in endurance time during cycling exercise tests at a constant work rate as the primary outcome measure.31

In IPF, no study evaluating differences between baseline and week 26 6MWD has ever found a significant difference between the pulmonary rehabilitation and usual care groups.19 The FITNESS study is the first to demonstrate a significant improvement in week 26 6MWD among patients with IPF. The findings suggest that the combination of initial 12-week rehabilitation with nintedanib and subsequent maintenance of pulmonary rehabilitation facilitates maintenance of the beneficial effects until week 26. Some reports suggest that maintenance rehabilitation programmes can improve exercise capacity in COPD over the long term;22 however, a systematic review concluded that the effects remained uncertain as of that time.33 The results of this study clearly indicate that the effect of pulmonary rehabilitation is lost after 26 weeks; one possible reason for this is the presence of patients with low compliance to rehabilitation. In fact, the low compliance group showed a significant worsening of 6MWD, while the high compliance group maintained an improvement in 6MWD (online supplemental e-Figure 2). Improving compliance with rehabilitation is likely to be an important issue in maintaining the effectiveness of long-term rehabilitation. Another possible reason is that the effect of rehabilitation may have been negated by a decrease in exercise capacity due to disease progression. In terms of the safety of pulmonary rehabilitation, there was no significant difference in suspected pulmonary rehabilitation-related cardiovascular or orthopaedic adverse events between the two groups. Our present findings on nintedanib-related and IPF-related adverse events are consistent with those of previous studies.

This study has some limitations. First, the pulmonary rehabilitation group was not blinded to the treatment, nor were they blinded to the assessors. This could have affected the results. To minimise the impact of unblinding in this study, fixed procedures were prepared to objectively assess outcomes and assessors were pretrained to be equal across sites. Second, the subjects were required to record the status of self-training at home in a diary, as a means to maintain the exercise load intensity of the maintenance pulmonary rehabilitation programme following induction.
pulmonary rehabilitation. However, it was difficult to quantify the load actually being applied. To monitor the exercise intensity of the maintenance pulmonary rehabilitation programme, a remote monitoring system may be employed in the future. Third, the pulmonary rehabilitation programme used was originally developed for patients with COPD; a programme needs to be developed specifically for IPF. Future studies are needed to determine whether patients with IPF, a restrictive disorder and COPD, an obstructive disorder, may be rehabilitated using the same programme and load configuration. Fourth, it is unclear whether the same results would be obtained for patients who do not meet the eligibility criteria (6MWD, mMRC grade and pulmonary function, among others) adopted in this study, for example, those with FVC less than 50%, mMRC grade 4, etc.

Table 2  Comparison of changes between baseline and each evaluation point in the two groups

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th></th>
<th>26 weeks</th>
<th></th>
<th>52 weeks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference† (SE)</td>
<td>P value</td>
<td>Difference† (SE)</td>
<td>P value</td>
<td>Difference† (SE)</td>
<td>P value</td>
</tr>
<tr>
<td>6 min walking distance</td>
<td>22.5 (10.1)</td>
<td>0.029</td>
<td>31.7 (12.5)</td>
<td>0.013</td>
<td>20.7 (23.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Endurance time</td>
<td>344.1 (62.9)</td>
<td>&lt;0.0001</td>
<td>271.0 (77.2)</td>
<td>0.0007</td>
<td>186.8 (77.9)</td>
<td>0.019</td>
</tr>
<tr>
<td>6 min walking distance, percentage of change</td>
<td>0.07 (0.02)</td>
<td>0.0068</td>
<td>0.08 (0.03)</td>
<td>0.0055</td>
<td>0.06 (0.05)</td>
<td>0.28</td>
</tr>
<tr>
<td>SGRQ total</td>
<td>−1.03 (2.34)</td>
<td>0.66</td>
<td>1.25 (2.74)</td>
<td>0.65</td>
<td>−0.20 (3.72)</td>
<td>0.96</td>
</tr>
<tr>
<td>SGRQ symptoms</td>
<td>−1.12 (3.43)</td>
<td>0.75</td>
<td>−0.71 (3.74)</td>
<td>0.85</td>
<td>−5.48 (4.34)</td>
<td>0.21</td>
</tr>
<tr>
<td>SGRQ activity</td>
<td>−1.86 (2.96)</td>
<td>0.53</td>
<td>0 (3.19)</td>
<td>1.00</td>
<td>0.52 (4.17)</td>
<td>0.90</td>
</tr>
<tr>
<td>SGRQ impact</td>
<td>−0.89 (2.8)</td>
<td>0.75</td>
<td>1.96 (3.33)</td>
<td>0.56</td>
<td>0.66 (4.31)</td>
<td>0.88</td>
</tr>
<tr>
<td>COPD assessment test</td>
<td>−1.36 (1.24)</td>
<td>0.28</td>
<td>−0.15 (1.54)</td>
<td>0.92</td>
<td>−0.97 (1.64)</td>
<td>0.55</td>
</tr>
<tr>
<td>Pedometer, step</td>
<td>274 (401)</td>
<td>0.50</td>
<td>546 (394)</td>
<td>0.17</td>
<td>540 (480)</td>
<td>0.26</td>
</tr>
<tr>
<td>Transitional Dyspnoea Index</td>
<td>2.32 (0.66)</td>
<td>0.0005</td>
<td>1.97 (0.66)</td>
<td>0.0035†</td>
<td>1.46 (0.67)</td>
<td>0.032</td>
</tr>
<tr>
<td>Dyspnoea-12</td>
<td>−0.48 (1.01)</td>
<td>0.63</td>
<td>0.58 (1.16)</td>
<td>0.62</td>
<td>1.35 (1.51)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale, Depression</td>
<td>0.03 (0.61)</td>
<td>0.96</td>
<td>−0.16 (0.60)</td>
<td>0.79</td>
<td>0.31 (0.65)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale, Anxiety</td>
<td>0.41 (0.60)</td>
<td>0.50</td>
<td>−0.2 (0.67)</td>
<td>0.60</td>
<td>0.56 (0.74)</td>
<td>0.45</td>
</tr>
<tr>
<td>Saturation of percutaneous oxygen (SpO₂), stable</td>
<td>0.44 (0.30)</td>
<td>0.15</td>
<td>0.42 (0.34)</td>
<td>0.22</td>
<td>0.55 (0.47)</td>
<td>0.24</td>
</tr>
<tr>
<td>SpO₂, lowest</td>
<td>−0.64 (1.12)</td>
<td>0.57</td>
<td>−0.44 (1.07)</td>
<td>0.69</td>
<td>0.07 (1.20)</td>
<td>0.95</td>
</tr>
<tr>
<td>FVC</td>
<td>0.69 (1.64)</td>
<td>0.68</td>
<td>1.08 (1.65)</td>
<td>0.51</td>
<td>−1.61 (1.80)</td>
<td>0.37</td>
</tr>
<tr>
<td>DLCO</td>
<td>NA</td>
<td>NA</td>
<td>−1.09 (3.79)</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Positive value indicates that the pulmonary rehabilitation group is better.

DLCO, diffuse capacity for carbon monoxide; FVC, forced vital capacity; NA, not applicable; SGRQ, St. George’s Respiratory Questionnaire.

Table 3  Adverse events observed during the study period

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary rehabilitation group (n=45)</th>
<th>Control group (n=43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–2</td>
<td>Grades 3–5</td>
<td>Grades 1–2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>30 (67%)</td>
<td>3 (7%)</td>
<td>31 (72%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (20%)</td>
<td>0</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (11%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Liver enzyme elevation</td>
<td>12 (27%)</td>
<td>0</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11 (24%)</td>
<td>0</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>2 (4%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>2 (4%)</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Progression of IPF</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Acute exacerbation of IPF</td>
<td>0</td>
<td>5 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>2 (4%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

Data indicate n (%) of the patients. P values were calculated for the difference between the pulmonary rehabilitation and control groups for the number of events of all grades. IPF, idiopathic pulmonary fibrosis.
Future studies are needed to identify patients who may benefit from this treatment strategy. Fifth, considering the decline in exercise capacity shown at week 52 in the pulmonary rehabilitation group, a larger sample size will be needed to detect the long-term effect. Finally, because of the mandatory use of nintedanib in this study, the results may not be applicable to patients for whom nintedanib is not used or in countries with restrictions on the use of nintedanib. However, in a long-term study of IPF, it would be difficult not to administer antifibrotic agents, which is the recommended treatment.

In conclusion, the combination of nintedanib and pulmonary rehabilitation in patients with IPF resulted in no difference in 6MWD compared with usual care with nintedanib, but a better outcome for endurance time. Further studies with strategies such as sophisticated long-term maintenance programmes are needed before pulmonary rehabilitation with nintedanib can be recognised as a robust care protocol for patients with IPF.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Nagasaki University Hospital (approval number: 17082190). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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Kindai University Faculty of Medicine
Kanagawa Cardiovascular and Respiratory Center
KKR Takamatsu Hospital
Kirioka Tsuda Hospital
Kobe City Medical Center General Hospital
Kobe City Medical Center West Hospital
Ogaki Municipal Hospital
Nagoya University Hospital
Nagasaki University Hospital
Saiseikai Kumanoto Hospital
Kameda Medical Center
Matsumoto Kyoritsu Hospital
Ise Red Cross Hospital
Kurashiki Central Hospital
Fujita Health University Hospital
Matsusaka Municipal Hospital
KKR Sapporo Medical Center
Seirei Mikatahara General Hospital
III. SUPPLEMENTARY FIGURES

Supplementary eFigure 1

The mean value of the Transition Dyspnea Index in the pulmonary rehabilitation (PR) and Control groups. Error bars indicate the standard error. The Transition Dyspnea Index was significantly better in the PR group at all evaluation points.

PR=pulmonary rehabilitation.
Supplementary eFigure 2

The mean change in 6-min walk distance (6MWD) from baseline to week 52 in the good and poor PR compliance groups. Error bars indicate the standard error.

The changes in 6MWD from baseline to week 52 in the good compliance (n=21) and poor compliance (n=19) group were -8 m (95% CI, -47 to 31) and -106 m (95% CI, -172 to -40), respectively.
IV. FINAL PROTOCOL

CJLSG 1601
Long-term effect of pulmonary rehabilitation under nintedanib in idiopathic pulmonary fibrosis (FITNESS)

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</table>
1 Introduction
All researchers involved in this research will comply with the Declaration of Helsinki (revised October 2013) and the Ethical Guidelines for Medical Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No. 3, 2014).

2 Background
Idiopathic pulmonary fibrosis (IPF) is one of the most common forms of idiopathic interstitial pneumonia, accounting for 50–60% of patients with interstitial pneumonia of unknown origin. The prognostic factors of IPF are poor pulmonary function, worsening of respiratory symptoms, worsening of physical activity, and development of acute exacerbations.13 The goal of IPF treatment is to improve prognosis, but no single drug therapy has been shown to improve prognosis. On the other hand, prevention of acute exacerbations and improvement of exercise capacity may improve the prognosis. A short-term pulmonary rehabilitation (PR) program of nine to 10 weeks has been reported to produce short-term improvements in exercise capacity and health-related quality of life in patients with IPF, but these improvements are not sustained and disappear after 26 weeks.24–26 More recently, exercise duration as measured by a bicycle ergometer has been reported to be the most sensitive indicator of the effectiveness of PR in patients with IPF.15

It is expected that the addition of a long-term maintenance rehabilitation program to a short-term PR program can maintain the effects of long-term improvement in exercise capacity and health-related quality of life, and the effects of six months to one year of PR have been reported in a few cases. In a few cases, the effects of PR for six months to one year have been reported.25,26 In order to maintain a long-term maintenance rehabilitation program, it will be important to slow the progression of IPF and reduce the frequency of acute exacerbations. The antifibrotic drug nintedanib has been shown to reduce respiratory depression in clinical trials in IPF, and has shown promise in preventing the onset of acute exacerbations and deterioration in health-related quality of life.17,25,26 It is hoped that the combination of nintedanib with IPF will allow patients to continue their rehabilitation program longer and maintain the improvement in exercise capacity longer.

3 Objectives
The purpose of this study is to evaluate the efficacy and safety of a short-term PR program followed by long-term maintenance rehabilitation in patients with IPF in combination with nintedanib. An open-label, multicenter, parallel-group, randomized, controlled trial will determine if there is a difference in the change in 6-minute walking distance (6MWD) between groups A and B at 52 weeks.

Group A: Continue oral nintedanib only
Group B: Concomitant programmed long-term rehabilitation under oral nintedanib

4 Methods
4.1 Study design
- Inclusion: Minor
- With or without intervention: With intervention
- Type of study: Randomized study
- Blinding of the study: open

4.2 Outline of research
Patients with stable IPF who have been taking nintedanib for at least 4 weeks and are able to attend outpatient rehabilitation twice weekly for the first 12 weeks and then every 2 to 4 weeks for 52 weeks will be assigned to one of the following two groups:

- Group A: Continue oral nintedanib only
- Group B: Concomitant programmed long-term rehabilitation under oral nintedanib

The duration of treatment will be 52 weeks for both groups.
4.3 Study drug
[Nintedanib]

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofev 150mg soft capsules</td>
<td></td>
</tr>
<tr>
<td>Ofev 100mg soft capsules</td>
<td></td>
</tr>
</tbody>
</table>

Manufactured by Nippon Boehringer Ingelheim Co.

[Insurance coverage or not]
The subjects of this study were patients with indications for nintedanib and respiratory rehabilitation, and the dose used was within the insurance coverage.

4.4 Inclusion/Exclusion criteria

[Inclusion criteria]
Patients who meet all of the following criteria are eligible.
1. Age range 40 to 80 years at the time of consent.
2. The IPF diagnosis is confirmed at each institution with reference to the 2011 guidelines and INPULSIS study criteria (see 4.4.1).
3. Previous 6-minute walking distance (6MWD) of 200 m or more and less than 600 m.
4. Dyspnea on exertion (modified Medical Research Council scale 1-3) (see 4.2).
5. Stable without infection or acute worsening within 3 months of enrollment.
6. Receiving nintedanib (150 mg or 100 mg twice daily) for at least four weeks before enrollment and expected to continue able to receive the drug for more than 12 months after registration thereafter.
7. Outpatients able to undergo rehabilitation twice a week for 12 weeks and once every two to four weeks in the subsequent 40 weeks.
8. Be able to perform exercise therapy as directed and record it in a diary.
9. Accurately answer the Patient Reported Outcome Questionnaire.
10. Percent forced vital capacity (FVC) ≥ 50%, 70% ≥ % diffusing capacity for carbon monoxide (DLCO) ≥ 30%, and forced expiratory volume in the first second (FEV1)/FVC ≥ 70% on a pulmonary function test performed within 1 month of registration.
11. Informed consent is obtained in writing from the individual.

[Reason for setting]
1. Because young-onset (<40 years) IPF patients are likely to be heterogeneous in the nature of their disease from general IPF patients due to factors such as genetic predisposition, we defined the age of the patients as 40 years or older. In addition, because patients older than 80 years can be expected to have difficulty with outpatient PR.
2. Because it is a generic diagnostic criterion that has been used in previous large-scale clinical trials.
3. Outpatient PR is considered difficult for patients who walk less than 200 m. Patients who can walk longer than 600 m have little need for PR.
4. The same concept as in 3), criteria for selecting a "patient population with good indications for outpatient PR."
5. In order to compare the data from the fixed-point evaluation, we thought that patients in the stable phase should be included.
6. The patient must be able to take nintedanib, which is the underlying concept of the study.
7. The patient must be able to attend outpatient rehabilitation, which is the fundamental concept of the study.
8. The patient must be able to attend outpatient rehabilitation, which is the fundamental concept of the study.
9. Because a questionnaire-type evaluation item is set as a secondary evaluation item.
10. The minimum value was set because it is predicted to be difficult to assess at 12 months if the IPF disease is too advanced. Because there is no proven benefit of rehabilitation therapeutic intervention for patients with mild disease, such as those with %DLCO >80%.
11. We would like you to cooperate in the research with full understanding and consent of the significance and risks of this research.

[Exclusion Criteria]
1. Patients will be excluded if any one of the following applies
2. Have collagen disease, known neuromuscular disease or other orthopedic disease that may affect assessment of exercise tolerance or training, or any other condition requiring exercise restriction at the time of enrollment.
3. A history of PR within the past 12 months. (This does not apply to acute or other short term conditions)
4. Receipt of systemic corticosteroids at a dose equivalent to more than 15 mg of prednisolone per day and/or immunosuppressants within 3 months before enrollment.
5. Has used pirfenidone within 3 months.
6. Presence of cardiac complications within 1 month of enrollment (unstable angina, myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting) or cerebrovascular disease within 6 months of enrollment.
7) Antiarrhythmic therapy is required.
8) Clinically complicated by severe pulmonary hypertension.
9) ALT and AST greater than two times the upper limit of the institutional reference range (ULN) at the time of enrollment.
10) At the time of enrollment, total bilirubin is greater than twice the ULN.
11) Creatinine clearance calculated by the Cockcroft-Gault formula is less than 30 mL/min at the time of registration.
12) Treated with fibrinolytic agents, anticoagulants at adequate therapeutic doses (e.g., vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin), or high-dose antiplatelet agents
13) Women who are pregnant or who may become pregnant.
14) Unable to perform the 6-minute walk test for any reason.
15) The investigator determines that the Investigator is not appropriate for enrollment in this study.
16) Patients with malignancies that have not been confirmed as recurrence-free for at least 3 years.

Note 1: Creatinine clearance = (140 - age) x weight (kg) x 0.85 (for women) / (72 x serum creatinine (mg/dL))

Note 2 Prophylactic administration of low-dose heparin (e.g., enoxaparin 4000 IU/day subcutaneously) or heparin flush required to maintain IV equipment, and prophylactic administration of antiplatelet agents (acetylsalicylic acid up to 325 mg/day and/or or clopidogrel 75 mg/day, and/or equivalent doses of other antiplatelet agents) may be administered.

[Reason for setting]
1) Because the result of the 6-minute walk test, which is the primary endpoint, are strongly affected by conditions other than IPF, and the effect of PE cannot be evaluated.
2) Because the effect of previous rehabilitation will be a modifying factor and cannot be proved to be purely the effect of this study.
3) Because it is recommended not to use as a treatment for IPF in the stable phase.
4) Because it will be difficult to prove that the effect is purely due to this study if the same drug is used.
5) To ensure the safety of the research subjects in performing rehabilitation.
6) To ensure the safety of the research subjects in performing rehabilitation.
7) To ensure the safety of the research subjects in performing rehabilitation.
8) Because nintedanib cannot be used safely.
9) Because nintedanib cannot be used safely.
10) Because nintedanib cannot be used safely.
11) Because nintedanib cannot be used safely.
12) Because nintedanib cannot be used safely.
13) The results of the 6-minute walk test, which is the primary endpoint, will be strongly affected by conditions other than IPF, making it impossible to evaluate the effect of respiratory rehabilitation.
14) To leave room for researchers and others to exclude ineligible patients in ensuring the safety of research subjects and in conducting the research properly.
15) Because it is intended for patients with stable disease states.

Criteria and definitions used in this study

4.4.1 IPF diagnostic criteria

For IPF diagnosis at each institution, the 2011 ATS/ERS/JRS/ALAT guidelines will be followed. For HRCT, the criteria of the INPULSiS study will be referred.

HRCT Findings (INPULSiS Study Criteria) Multiple Choice

| A | Definite honeycomb lung destruction with basal and peripheral predominance |
| b | Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance |
| C | Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern |

Patients who meet HRCT criteria A, B and C or A and B or C and B and C are eligible for study entry even if a surgical lung biopsy is not available. If a surgical lung biopsy is obtained, histology will be confirmed according to ATS/ERS/JRS/ALAT 2011 guidelines. If the HRCT pattern is "definite UIP" but the surgical lung biopsy shows "definite UIP" or "probable UIP", the patient may be eligible for registration as "consistent with the diagnosis of IPF" after multidisciplinary discussion.

4.4.2 Degree of dyspnea on exertion Modified Medical Research Council (mMRC) grade

<table>
<thead>
<tr>
<th>grade</th>
<th>Degree of the breathlessness related to activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I only get breathless with strenuous exercise.</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying on the level or walking up a slight hill.</td>
</tr>
<tr>
<td>2</td>
<td>I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.</td>
</tr>
</tbody>
</table>
4.5 Study period
Date of approval by the director of each joint research facility - April 30, 2021 (Registration deadline: December 31, 2019)
### 4.6 Summary of protocol visit and assessments

<table>
<thead>
<tr>
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<th>Inclusion</th>
<th>Baseline -4w</th>
<th>12w±14d</th>
<th>26w±14d</th>
<th>40w±14d</th>
<th>52w (50 w-56w)</th>
</tr>
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<tr>
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<tr>
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<td>Resting SpO₂</td>
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<td>⬤</td>
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<tr>
<td>6MWT</td>
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<td>⬤</td>
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<tr>
<td>Exercise duration</td>
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<td>⬤</td>
<td>⬤</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>Respiratory function test (FVC)</td>
<td>Within 1 month</td>
<td>.</td>
<td>⬤</td>
<td>.</td>
<td>.</td>
<td>⬤</td>
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<tr>
<td>Respiratory function test (DLco)</td>
<td>Within 1 month</td>
<td>.</td>
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<td>Health status (SGRQ, CAT)</td>
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<td>⬤</td>
<td>⬤</td>
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<tr>
<td>Anxiety and Depression (HADS)</td>
<td>.</td>
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<tr>
<td>modified MRC</td>
<td>⬤</td>
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</tr>
<tr>
<td>dyspnea (BDI/TDI, Dyspnea-12)</td>
<td>.</td>
<td>⬤</td>
<td>⬤</td>
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<tr>
<td>Physical activity (number of steps)</td>
<td>.</td>
<td>⬤</td>
<td>⬤</td>
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<td>ECG</td>
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<td>⬤</td>
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<td>blood chemistry test</td>
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<td>⬤</td>
<td>⬤</td>
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<tr>
<td>Nintedanib medication status</td>
<td>.</td>
<td>.</td>
<td>during the study period</td>
<td>.</td>
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<td></td>
</tr>
<tr>
<td>Rehabilitation diary (Group B only)</td>
<td>.</td>
<td>.</td>
<td>during the study period</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>LTOT status</td>
<td>⬤</td>
<td>.</td>
<td>during the study period</td>
<td>.</td>
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<tr>
<td>adverse event</td>
<td>.</td>
<td>.</td>
<td>at any time</td>
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<tr>
<td>unscheduled hospitalization</td>
<td>.</td>
<td>.</td>
<td>at any time</td>
<td>.</td>
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</tbody>
</table>

At the evaluation points (previous evaluation, mid-term evaluation (1), mid-term evaluation (2), mid-term evaluation (3), and final evaluation), the stipulated evaluation is carried out.

<table>
<thead>
<tr>
<th>Evaluation point</th>
<th>From the test introduction</th>
<th>Allowances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline evaluation</td>
<td></td>
<td>Minus 28 days - allocation</td>
</tr>
<tr>
<td>Mid-term evaluation</td>
<td>12 weeks, 26 weeks, 40 weeks</td>
<td>Minus 14 days to plus 14 days</td>
</tr>
<tr>
<td>Final evaluation</td>
<td>52 weeks</td>
<td>Minus 14 days to plus 28 days</td>
</tr>
</tbody>
</table>

Note: “minus 4 days to plus 14 days” means “the same day of the week two weeks ago to the same day of the week two weeks later”.

If the data cannot be evaluated within the allowable range, it shall be treated as missing data.

### 4.7 Items to be collected in the study

- Patient background: sex, date of birth, age, height, weight, smoking history, average number of cigarettes smoked per day, total number of years smoked, year of IPF diagnosis, presence of surgical lung biopsy, date of nintedanib initiation, daily nintedanib dose, mMRC, medical history, comorbidities, presence and content of concomitant medication for IPF other than nintedanib details, presence of oxygen therapy and its setting (rest, exertion, sleep)
- CT patterns in HRCT (INRULSIS criteria)
- Arterial blood gas analysis date of examination, oxygen inhalation conditions at the time of examination, PaO₂, PaCO₂
- Resting SpO₂ test date, oxygen conditions at test
- 6MWT date of examination, oxygen conditions at the time of examination, walking distance, minimum SpO₂ after
examination:
- Steady-state loading test using a bicycle ergometer. Date of examination, oxygen inhalation conditions at the time of examination, exercise duration.
- Pulmonary function test date of examination, age at examination, height at examination, weight at examination, FVC (forced vital capacity), FEV1/FVC, DLco (lung diffusing capacity).
- Quality of Life Scale. SGRQ test date, SGRQ score, CAT test date, CAT score.
- Anxiety and Depression Scale (HADS) test date, HADS score.
- Dyspnea scale BDI test date, BDI score, Dyspnea-12 test date, Dyspnea-12 score.
- Pedometer average number of steps per day.
- Electrocardiogram date of examination, presence of abnormal findings.
- Blood test date of examination, white blood cell count, hemoglobin, hematocrit, platelet count, albumin, creatinine, AST, ALT, total bilirubin, ALP, GGT, LDH, CRP, K<sub>L</sub>-6.
- Nintedanib medication status record daily medication status in the prescribed medication diary.
- Rehabilitation diary (Group B only) The status of daily respiratory rehabilitation is recorded in the prescribed rehabilitation diary.

4.8 Prohibited matters
Interventional trials other than this study
Start smoking
Chronic non-prescribed rehabilitation

Pirfenidine (If pirfenidine is used when there is further progression of IPF after discontinuation of nintedanib due to difficulty in continuation, treat as a deviation from protocol)

4.9 Concomiantly restricted drugs/Concomitantly restricted therapy
1) Long-term oxygen therapy (LTOT) and home non-invasive positive pressure ventilation
Long-term oxygen therapy (LTOT) and home noninvasive positive pressure ventilation may be introduced or modified or withdrawn as the investigator deems appropriate, for training during the rehabilitation program in group B. LTOT patients should use oxygen at a set flow rate on exertion.
2) Treatment of acute exacerbations of IPF.
During and after acute exacerbations of IPF, all treatment options other than pirfenidine, including new steroid initiation, dose modification, and immunosuppressive agents, as deemed appropriate by the investigator, will be available. The dosage and administration of steroids and immunosuppressive agents will be left unchanged whenever possible, except in the case of acute exacerbations or other urgent requirements.
3) Rehabilitation for acute phase
Both groups, if the condition is judged to be acute, rehabilitation limited to the acute phase can be performed. However, if it is judged to be a chronic condition, rehabilitation in group A should be limited to ADL training and prevention of disease, not programmatic intervention. In group B, the prescribed long-term rehabilitation program should be continued as much as possible.

4.10 Provisions for dose reduction and drug withdrawal
Nintedanib oral administration may be suspended or reduced at the discretion of the investigator in accordance with the latest product insert. The dose may be increased to 150 mg twice daily depending on the patient's condition. If the dose discontinuation criteria (rather than the temporary interruption criteria) in the package insert are met, the drug will not be re-dosed. If nintedanib is discontinued, the study will continue and will be assessed as prescribed at the pre-specified assessment points.
The usual adult dosage of nintedanib is 150 mg twice daily orally after breakfast and dinner. Depending on the patient's condition, the dosage may be reduced to 100 mg of nintedanib twice daily.
Precations for use related to dosage and administration
1. If adverse reactions such as diarrhea, nausea, vomiting, etc. are observed, after appropriate measures such as symptomatic treatment, a reduction in the dose or interruption of treatment should be considered until the patient recovers to a state in which treatment with this drug is possible. When resuming treatment after interruption, consider resuming treatment at a dose of 100 mg twice daily. Depending on the patient's condition, the dose may be increased to 150 mg twice daily. When re-administering or increasing the dose, administer with caution and monitor the patient's condition closely after administration.
2. If AST or ALT exceeds three times the upper limit of the reference value, the dosage of this product should be reduced or the treatment should be interrupted, and the patient should be carefully monitored. If treatment is interrupted and then resumed, the dosage should be started at 100 mg twice daily after the AST or ALT level has recovered to the level before treatment. The dose may be increased to 150 mg twice daily depending on the patient's condition. If the dose is to be re-administered or increased, it should be administered with caution, and the patient's condition should be monitored closely after administration.
Criteria for discontinuing or suspending/resuming a long-term rehabilitation program
The Group B rehabilitation program will be conducted in accordance with the separately attached procedure. If, in the judgment of the investigator, the rehabilitation program should not be conducted, it will be suspended (skipped). The period of the intensive program may be extended up to 14 days (the same day of the week two weeks later), but it will not be extended beyond that time, and the patient will be transferred to the maintenance program thereafter.

In both groups, regardless of the cessation or discontinuation of protocol treatment (i.e., cessation or discontinuation of nintedanib medication or rehabilitation), the study will continue and the prescribed assessments will be performed at the predetermined assessment points (baseline evaluation, mid-term evaluation, and final evaluation). If the prescribed evaluation cannot be performed, the reason will be left in the description.

<table>
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<td>Minus 14 days to plus 28 days</td>
</tr>
</tbody>
</table>

Note: "minus 14 days to plus 14 days" means "the same day of the week two weeks ago to the same day of the week two weeks later".
Set the allowable range as described above. If the data cannot be evaluated within the allowable range, it shall be treated as missing data.

4.11 Other treatment options
In Japanese guidelines, only nintedanib monotherapy and pirfenidone monotherapy are recommended at a moderate or higher level of evidence for the treatment of chronic stable IPF. The quality of the evidence level for recommendations/disrecommendations for other medications, oxygen therapy, and respiratory rehabilitation is low. Although not necessarily guideline-compliant, treatment other than nintedanib monotherapy and pirfenidone monotherapy may be chosen on a case-by-case basis in consultation with the patient and the investigator.

4.12 What to do after the research is completed
No provision will be made for treatment after the completion of this research. Thereafter, we will provide medical care that we consider most appropriate for the research subjects.

5 Discontinuation criteria for individual research subjects
5.1 Stopping point
- If a lung transplant is performed
- When the researcher, etc. judges the continuation of the research on the research subject to be inappropriate due to the occurrence of an adverse event (exacerbation of the primary disease, worsening of a complication, new complication of disease, etc.)
- When the research subject requests discontinuation of the research due to reasons that cannot be denied to be related to adverse events.
- When the research subject requests discontinuation of the study for reasons that can be ruled out as being related to the adverse event (this classification is used only when the relationship to the adverse event can be first ruled out, such as the moving of the subject or household members).
- Death during protocol treatment (death before the decision to discontinue protocol treatment for other reasons)
- Other cases in which the investigator considers it difficult to continue the protocol. Exacerbation prior to the start of enrollment treatment (protocol treatment could not be started due to acute exacerbation), found to be in violation of the protocol, or found to be ineligible due to a change in diagnosis after enrollment.

5.2 What to do when research is discontinued
If any of the above criteria is met, the researcher, etc. will discontinue the research with respect to the research subjects concerned. In such cases, explanations will be given to the research subjects as necessary. The treatment of research subjects after discontinuation will be handled so as not to be detrimental to the research subjects.

6 Case registration and allocation methods
Assignment method: random assignment / minimization method
Dynamic allocation adjustment factors: (1) distance walked on the 6MWT performed as a pre-assessment after enrollment (≥350m), (2) institution, (3) %FVC within 1 month before enrollment (≥70%) Organization for registration and allocation: Data Center: Center for Advanced Medical Care and Clinical Research, Nagoya University Hospital
[How to register cases] Enrollment is possible if all eligibility criteria (see 4.4) are met and none of the exclusion criteria (see 4.4) are violated.
an electronic data capture (EDC) system is used. The data center confirms whether registration is possible and, if so, sends the results of the completed case registration to the enrolling site. The data center will also inform the research secretariat (representative, administrative staff, and medical staff) of the results of registration, regardless of whether registration is possible or not.

6.1 Registration to allocation and trial introduction
A baseline assessment (see 4.7) including a 6MWT and endurance time will be performed from enrolment to 4 weeks.
[Assessment of physical activity (number of steps) (baseline assessment)]
At the time of registration, a pedometer with a new battery and initial settings is lent out, and instructions on how to use it are given. At the same time, a pedometer recording form is handed to the participant and he or she is instructed on how to record the data. The pedometer should be worn every day (from waking to sleeping) from the day after it is handed over. However, if the patient forgets to wear the pedometer or the measurement is faulty, the data will not be used as the day of faulty measurement, but will be supplemented with the data of the sixth day of the following day, so that the data will be collected for a total of five days. If there are multiple measurement failure days, the data for the seventh day, the eighth day, and so on (the ninth, tenth, and so on days) are used as supplementary data. It is not intentional to pick up data collection days for supplementary data. However, if there is a missing entry, it is possible to collect data using the memory function of the pedometer.

After completion of the baseline assessment, the data center will perform allocation according to the information entered in the EDC. Random assignment will be done using a minimization method that uses (1) distance walked (<\= 350 m), (2) facility, and (3) %FVC (<\= 70%) as adjustment factors to avoid large bias in the 6MWT. Detailed procedures for random assignment will not be known to investigators at study participating sites.
[Dynamic allocation adjustment factor:]
(i) Walking distance of 6MWT performed as a pre-assessment after enrollment (<\= 350m)
(2) Facilities
(iii) %FVC within 1 month prior to registration (<\= 70%)
[From allocation to start of study treatment]
The data center will randomly assign patients to Group A or Group B, and the results of the assignment will be sent to the enrolment sites.
Patients in Group A will continue to receive nintedanib and receive their usual outpatient treatment; patients in Group A will have the same allocation and study entry date.
Group B will continue to take nintedanib and also begin a long-term rehabilitation program. The long-term rehabilitation program will begin within 2 weeks of assignment (by the same day of the following week), and the first day of rehabilitation will be the study entry date.

It is at the discretion of the investigator whether to initiate or discontinue protocol treatment if clinical laboratory values or other data deteriorate after enrollment and before the start of treatment and no longer meet the eligibility criteria.

7 Evaluation items (endpoints)
7.1 Primary endpoint
Comparing Group A and Group B
Change from baseline assessment in walking distance for the 6-minute walk test (6MWT) at the final assessment

7.2 Secondary endpoint
Main secondary endpoint:
Comparing Group A and Group B
(i) Change from the baseline in the endurance exercise time measured using the bicycle ergometer at the final assessment
Other secondary endpoints:
Comparing Group A and Group B
(i) Change in the total score of the St. George's Respiratory Questionnaire Japanese Version 2 (SGRQ) at the final evaluation from the baseline
(ii) Percentage change from baseline in walking distance at 6MWT at final assessment
(iii) Physical activity (steps), SGRQ component scores, COPD Assessment Test (CAT), dyspnea (Transitional Dyspnea Index (TDI), Dyspnea-12), and Hospital Anxiety and Depression Scale (HADS) at the final assessment. Depression Scale (HADS) from the baseline.
(iv) Change from baseline in FVC, DLco, and SpO2 (at rest and immediately after 6MWT) at final assessment
(v) Mortality rates and frequency of unplanned hospitalizations up to the final assessment
(vi) Primary and secondary endpoints will be assessed at Mid-term assessment point (2) (Week 26)
Group B only
(vii) Compliance with programmed long-term rehabilitation in group B up to the time of the final assessment (the ratio of the number of times the program is implemented to the number of times it is scheduled to be implemented as specified)
(viii) Percentage of patients with good rehabilitation compliance who have a programmed long-term rehabilitation compliance of 70% or more in Group B up to the time of the final assessment
(ix) Change from baseline in walking distance of 6MWT at final assessment in subpopulations (≥70%, 70%<) by rehabilitation compliance

[Evaluation of physical activity (number of steps) (mid-term evaluation-1, mid-term evaluation-2, final evaluation)]
In the case of Group A, a pedometer with a new battery and initial settings will be lent to the participants so that they can start wearing it during the evaluation period, and they will be instructed on how to use it. At the same time, a pedometer recording form will be handed to the participants and they will be instructed on how to record the data.
In the case of Group B, the battery of the pedometer loaned for personal use will be replaced with a new one. In both groups, the pedometer is worn every day (from waking to sleeping) from the next day. However, if there is a case of forgetting to wear the pedometer or measurement failure, the data will not be used as the day of measurement failure, but will be supplemented by the sixth day of measurement failure, and data will be collected for a total of five days. If there are multiple measurement failure days, the data for the seventh day, the eighth day, and so on (the ninth, tenth, and so on days) shall be used as supplementary data. It is not intentional to pick up data collection days for supplementary data. However, if there is a no-called entry, it is possible to collect data using the memory function of the pedometer.

7.3 Safety evaluation items
Adverse events and unscheduled hospitalizations will be collected during the study period, and at defined endpoints, ECG, blood tests, and resting SpO2 used to evaluate the safety of the treatment compared to baseline.

[Priority safety endpoints]
For the following 12 items, as priority safety endpoints, "No occurrence" should be confirmed and entered on the EDC even if the event does not occur. Diarrhea, nausea, abdominal pain, liver enzyme increase, vomiting, anorexia, bleeding, acute coronary syndrome, stroke, arrhythmia, heart failure, acute exacerbation of IPF.
Adverse events other than the pivotal safety endpoints will be entered on the EDC as they occur.

[Degree of adverse event/adverse reaction]
Adverse events/adverse reactions should be evaluated in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Japanese translation of JCOG/JSCO (http://www.jcog.jp/SIRYOU/ctcae.html). Evaluation

[Unscheduled hospitalization.]
If there is an unscheduled hospitalization, the cause of the hospitalization (due to nintedanib side effects, rehabilitation complications, or otherwise) will be determined.

8 Sample size

8.1 Target sample size
The target number of enrolled cases for the entire study is 42 cases in group A and 42 cases in group B, totaling 84 cases.

[Rationale]
There are no previous studies evaluating the change in 6MWD when nintedanib is combined with a PR program. Although nintedanib treatment is expected to reduce worsening of the 6MWD, there are few studies on the extent to which nintedanib treatment changes or reduces worsening of the 6MWD. A maintenance PR program may maintain the efficacy of short-term PR programs in the long term, as has been reported in the past. In summary, we hypothesize that treatment with a programmed long-term PR program under nintedanib would be as effective as short-term PR.

Based on the four previous short-term PR studies for IPF described in the review reported by 11 Downman et al. in 2014, the standard deviation of the 6MWD pre- and post-difference was calculated to be 55 m. In this study, the expected value of the difference in the pre/post 6MWD between the nintedanib with and without long-term rehabilitation group was set at 36 meters. Based on the above, we calculated that the sample size required to show a significant difference at the primary endpoint with 80% power in a two-tailed test (5% level of significance) was 37 patients in each group, for a total of 74 patients. In anticipation of dropouts, we set a target of 42 patients per group for a total of 84 patients. As a result, this sample size was close to that of the HOPE IPF study 12. With this sample size, Cohen’s d was 0.65, which is between the medium effect (d = 0.5) and large effect (d = 0.8).

As for the main secondary endpoint, based on previous studies, the difference in pre/post cycle ergometer exercise duration between the nintedanib plus long-term rehabilitation group and the nintedanib without rehabilitation group is estimated to be 10 minutes with a maximum standard deviation of 10 minutes. Therefore, it is possible to detect the difference between the treatment groups at a significance level of 5% and a power of 90% or more by aggregating the target number of 84 cases.

9 Definition of the analysis target

9.1 Target population for analysis
The following table shows the treatment of research subjects for statistical analysis. In principle, the classification of subjects is determined according to the following criteria. For efficacy analysis, the largest analysis population will be used as the primary analysis subject. Safety analysis will be conducted in the safety analysis population.

| Registration example | Cases enrolled after the research secretariat confirmed the selection and exclusion |

p. 16
9.2 Definition of classification of cases
Eligible cases: cases that meet all of the selection criteria and none of the exclusion criteria
Discontinuation cases: Cases in which the study was discontinued according to the discontinuation criteria in 5.1.

9.3 Handling of data on discontinued cases, missing values, etc.
1) Handling of data on discontinued cases
   For FAS, the value actually measured up to the time of discontinuation is used for evaluation, regardless of the time of discontinuation.
   If the discontinuation period is less than 4 weeks from the start of treatment, the PPS is treated as a missing value.
   If the discontinuation period is 4 weeks or later, the actual measured value should be used.
2) Treatment of missing values in tests for determining treatment effects
   Because of the possible occurrence of missing values, the test will be analyzed using a repeated measures mixed effects model (MMRM). No explicit completion for missing values will be performed.
   In addition, in the summary of data at the specified evaluation points (baseline, mid-term evaluation 1, -2, -3, and final evaluation), if there is a gap in the observation date that exceeds the permissible range of the specified evaluation points, or if measurement values obtained by methods or conditions other than the default are treated as missing values (excluded from the scope), the method is also provided for reference. This is done for reference.

9.4 Analysis method
1) Breakdown of cases
   The number of FAS, PPS, and discontinued cases will be displayed along with the group identification.
2) Treatment status
   Compliance with the long-term rehabilitation program (ratio of the number of times the program is implemented to the number of times the program is scheduled to be implemented) will be calculated against the PPS.
3) Data summary
   Basic statistics (maximum, median, minimum, 25th percentile point, 75th percentile point, mean, and standard deviation) of the assessment points (baseline, mid-term assessment 1, mid-term assessment 2, mid-term assessment 3, and final assessment) will be calculated for each group for all test items obtained as continuous values.
   Data measured over time are shown in Box-Whisker plots with summaries of the assessment points (preassessment, mid-term assessment 1, mid-term assessment 2, mid-term assessment 3, and final assessment) for each group.
   For all test items that are available as categorical data, the categories will be aggregated by group and by assessment point.
4) Analysis of background factors
   The distribution of data for items obtained as continuous values such as age will be summarized according to 3). For items obtained as categorical data such as gender, smoking history, surgical lung biopsy (yes or no), etc., the categories will be summarized by group.
5) Analysis of the primary endpoint
   (1) Endpoint: Group A and B will be compared for the change in 6MWD at the baseline and the final assessment.
   (2) Time of evaluation: The time of final evaluation.
6) Analysis of the main secondary endpoint
   (1) Evaluation items: Group A and Group B will be compared in terms of the amount of change (in seconds) from the baseline evaluation in the endurance exercise time measured with a bicycle ergometer at the baseline and the final evaluation.
   (2) Time of evaluation: The time of final evaluation.
5) Methods of evaluation: Repeated measures mixed effects model (MMRM) will be used for analysis. The
interaction terms between exercise duration, treatment group, study time point, and treatment group and study time point in the previous assessment will be fixed effects, and the change in exercise duration will be the outcome variable. Adjusted means and 95% confidence intervals will be calculated for each treatment group and assessment time point. Significance level is 5% two-sided.

7) Analysis of other endpoints
   The significance level for each analysis is not adjusted for multiplicity and is 5% two-sided in all cases.
   (1) Change in total score of St. George's Respiratory Questionnaire (Version 2) (SGRQ) between pre- and final assessment, percentage change in 6MWD between baseline and final assessment, physical activity (steps), SGRQ component scores, COPD Assessment Test (CAT), dyspnea (Transitional Dyspnea Index (TDI), Dyspnea-12), Hospital Anxiety and Depression Scale (HADS), and changes in FVC, DLco, and SpO2 (at rest and after 6MWT) between the baseline and final assessments will be analyzed using a repeated measures mixed effects model (MMRM). The interaction terms for each measure at the baseline (excluding the percentage change in 6MWD), treatment group, study time point, and treatment group and study time point will be fixed effects. Adjusted means and 95% confidence intervals will be calculated for each treatment group and assessment time point.

   (2) Compliance with programmed long-term rehabilitation in group B (percentage of the number of doses administered to the number of doses scheduled to be administered as prescribed) until the final assessment will be calculated and Fisher's exact test will be applied.

   (3) The percentage of patients with good rehabilitation compliance in group B with a programmed long-term rehabilitation compliance of at least 70% until the final assessment will be calculated and Fisher's exact test will be applied.

   (4) A repeated measures mixed effects model (MMRM) will be used to analyze the change (m) in 6MWD at the final assessment of patients with good rehabilitation compliance comparison to the change in group A. The interaction terms between the 6-minute walk distance at the pre-assessment, the treatment group, the study time point, and the treatment group and study time point are fixed effects, and the change in the 6-minute walk distance is the outcome variable. Adjusted means and 95% confidence intervals will be calculated for each treatment group and assessment time point.

   (5) The Fisher's exact test is applied to the proportion of deaths up to the last assessment, and the Mann-Whitney test is applied to the frequency of unplanned hospitalizations.

   (6) The 6MWD and percentage change, SGRQ total score, each component score, physical activity, CAT, dyspnea (TDI, Dyspnea-12), HADS, FVC, and SpO2 (at rest and after 6MWT), which are to be assessed at mid-term assessment point-2. Repeated measures mixed effects model (MMRM) will be used to analyze the comparison of the observed changes.

   (7) For unscheduled hospitalizations, the date of admission, date of discharge, and primary cause of hospitalization will be tabulated in the following categories: acute exacerbation of IPF (unknown cause, secondary), chronic respiratory compromise, airway infection, pneumothorax/mediastinal emphysema, heart failure, ischemic heart disease, arrhythmia, non-airway infection, and other (free text). In addition, whether the unplanned hospitalization was due to nintedanib side effects or rehabilitation complications will be tabulated. The Mann-Whitney test will be applied to compare the frequency of unplanned hospitalizations by group.

8) Safety (adverse events)
   For ECG abnormalities, the occurrence of ischemic heart disease and arrhythmia requiring treatment will be counted as serious cardiac complications, and Fisher's exact test will be applied to compare the percentage of occurrence in each group. The Fisher's exact test will be applied to compare the incidence of each group. The test will be two-tailed and the significance level will be 5%. Other adverse events will be listed and Fisher's exact test will be applied to compare the incidence of each adverse event. The test will be two-tailed for each adverse event and the significance level will be 5%.

10 Informed consent
   10.1 How to obtain consent
[Explanation to the patient.]
Prior to enrollment, the investigator will provide the patient with a written and verbal explanation of the study that has been approved by the participating institution (either the explanatory document in the Appendix or the explanatory document modified by the participating institution and approved by the director). Technical terms and expressions should be avoided to the extent possible, and patients should be given sufficient time to consider their participation in the study.
After confirming that the patient has understood the information, the patient's free and voluntary consent must be obtained in writing.
It is possible that re-consent will have to be obtained if new findings are obtained. This should be done according to the communication from the secretariat.
[Obtain consent.]
The researcher will explain the following items to the research subjects themselves using an explanatory document.
After confirming that the subject patient fully understands the contents of this study, the researcher will obtain the
Supplemental material

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patient's written consent to participate in the study of his/her own free will. The researcher will hand a copy of the signed consent document to the subject patient. The original of the consent document will be kept by the researcher.

1. about clinical research
2. you are free to participate in clinical research
3. about the disease of which this study is a part
4. the purpose of the research
5. the nature of the research
6. other treatment methods
7. expected duration of the study and number of participants
8. expected benefits and disadvantages
9. what you must observe
10. the case of discontinuation of the research
11. information about the research

10.2 What to do when withdrawing consent

If the research subject withdraws consent to participate in the research, the researcher, etc. will ask the subject to sign a withdrawal of consent form and confirm the withdrawal of consent. The researcher, etc. who confirms the withdrawal of consent will enter a note to that effect in the medical record.

All data of research subjects who have withdrawn their consent will be removed from analysis, and all information will be destroyed.

11 Anticipated benefits and disadvantages (side effects/complications)

11.1 Benefit

There will be no direct benefit to the research subjects from participating in this study. Research results may contribute to future medical advances.

11.2 Disadvantages

In both groups, it will take an extra 60 minutes for each prescribed evaluation and a default number of hospital visits and outpatient examinations for this study; if assigned to group B, it will take about 90 minutes for each prescribed rehabilitation visit. There is no increase in the patient's own medical cost burden due to the rehabilitation program, as it is covered by the Japanese High Cost Medical Expense System. The complications of long-term rehabilitation programs are not fully known at present, but as with general exercise training, care must be taken to avoid acute coronary artery syndrome, stroke, arrhythmia, heart failure, and musculoskeletal disorders caused by excessive training.

11.3 Side effects/complications

Adverse reactions to nintedanib listed in the package insert include severe diarrhea (3.3%), hepatic dysfunction (0.9%), thromboembolism (0.5%), thrombocytopenia (frequency unknown), gastrointestinal perforation (0.2%), interstitial pneumonia (frequency unknown), decreased appetite (14.5%), diarrhea (67.1%), nausea (11.8%), elevated liver enzymes (27.6%), weight loss (5-10%), abdominal pain (5-10%), less than 5% (hypertension, vomiting, constipation, hyperbilirubinemia, rash, headache, bleeding). Commonly considered complications of PRT, all of which are rare in frequency, include acute coronary artery syndrome, stroke, arrhythmia, heart failure, and musculoskeletal disorders.

12 Termination or discontinuation

The principal investigator will consider whether or not to continue the research implementation if any of the following applies

• When significant information is obtained regarding the safety or other aspects of the treatment or evaluation methods to be implemented in the research.
• When it is judged to be extremely difficult to reach the planned number of cases due to difficulty in incorporating research subjects.
• When it is judged that it is ethically difficult to continue the research due to insufficient efficacy of the treatment implemented in the research.
• When the Ethics Review Committee recommends or directs that the research be discontinued.
• When the Ethics Review Committee instructs changes to the implementation plan, etc., and it is judged to be difficult to accept the changes.

In addition, if any of the following applies, the principal investigator shall report the decision to terminate or suspend the research to the director of the institution without delay, as well as a summary of the results of the research. After the decision to discontinue the study has been made, the decision will be promptly communicated to the Ethical Review Committee of the institution participating in the study and other relevant physicians, and they will

* 15 *

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be responsible for handling the situation after the discontinuation.

[End of this study]
- When it becomes clear that there is no medical significance in continuing the research.
- When the number of scheduled cases is reached.
- When the end of the scheduled period is reached.

13 Adverse events

13.1 Response to adverse events

If an adverse event is observed in a research subject during the period of this research, the researcher, etc. will immediately take appropriate measures and record the event in the medical record and case report form.

13.2 Definition of serious adverse events

Adverse events that fall under any of the following categories shall be considered "Serious Adverse Events" and shall be subject to urgent reporting.
- Death
- Cases that may lead to death
- Cases that require hospitalization or extended hospitalization for treatment
- Disability (permanent or significant impairment or dysfunction)
- Cases that may lead to disability
- Cases that are as serious as the cases listed in above
- Congenital diseases or anomalies in later generations

13.3 Response to the occurrence of serious adverse events

In the event of an adverse event that is the subject of an urgent report, the investigator must promptly inform the principal investigator of the research participating facility. If the principal investigator at the research participating site cannot be reached, the site coordinator or investigator must assume the responsibilities of the principal investigator at the research participating site.

Initial report

When an adverse event subject to an urgent report is observed, it should be immediately reported to the head of the research participating facility, and the principal investigator of the research participating facility should send a fax and make a phone call to the research secretariat according to the prescribed form with a summary within 72 hours of learning of the adverse event.

Secondary report

The principal investigator of the participating institution should mail or fax the prescribed form to both Takashi Ogura, the principal investigator, and the research secretariat within 15 days of learning of the adverse event. If an autopsy has been performed, the autopsy findings should also be attached.

13.4 Adverse events that are normally reportable

Adverse events that fall into any of the following categories are usually reportable.
1. Deaths occurring after 31 days from the date of last protocol treatment for which a causal relationship to protocol treatment cannot be ruled out. Clearly present illness deaths do not apply.
2. All adverse events during protocol treatment other than the adverse events with an urgent reporting requirement described above.

13.5 Normal reporting (excluding emergency reporting)

For serious adverse events that have a reasonable causal relationship with the protocol treatment, the principal investigator at the participating institution should fill out the "Treatment Progress Record" corresponding to the time of occurrence and send it to both Takashi Ogura, the principal investigator, and the research secretariat by mail, fax, or e-mail within 15 days of learning of the adverse event. Send the form by mail, fax, or e-mail within 15 days of learning of the adverse event. Other adverse events will be entered into the EDC system according to the timing of regular data collection.

14 Response to and compensation for damage to the health of research subjects

In the event that health damage occurs to a research subject as a result of this research, the researcher will take appropriate measures.

In the event that health damage occurs as a result of this research, treatment will be provided using the research subject's health insurance in the same manner as normal insurance treatment. Neither the organization/facility involved in this research nor individuals such as physicians will compensate the research subjects for out-of-pocket medical expenses, compensation for absence from work, or compensation for differential bed charges. For this research, we will
purchase clinical research insurance that provides the following compensation in case any health damage occurs to the research subjects.

In clinical research insurance, all persons involved in this clinical research, including the principal investigator, shall be insured (a person to whom the insurance is applied; hereinafter the same). The same shall apply hereinafter. This insurance shall cover the following damages incurred by the insured for bodily injury (including “death”) to the research subject from the start of the research to within one year after the end of the research. The insured person shall be compensated for the following losses incurred by the insured person with respect to bodily injury (including “death”) to the research subject from the start of the research until one year after the end of the research:

1. Damages incurred by the insured person as a result of assuming legal liability for the research subject (excluding cases arising from medical treatment).
2. Damages suffered by the insured as a result of the insurer assuming the responsibility for compensation for the research subjects' physical disability, for which a causal relationship with this research cannot be clearly denied, in accordance with the health damage compensation standards described in the explanatory document issued to the research subject.

"Health Damage Compensation Standards" shall be as follows.

In the event of death or physical disability corresponding to the first or second degree of permanent disability according to the classification in the enforcement order of the Pharmaceuticals and Medical Devices Agency Act, compensation determined by the principal investigator with reference to the benefits of the Adverse Drug Reaction Relief System will be paid.

15 Handling of personal information and information

15.1 Protection of personal information

We recognize that personal information, medical information, and other information related to privacy should be strictly protected and carefully handled under the principle of respect for the individual's personality, and we will take all possible management measures to protect privacy.

If the following applies, it shall be followed in addition.

Ethical Guidelines for Medical Research Involving Human Subjects (public notice issued on December 22, 2014, partially revised on February 28, 2017)

15.2 Handling of information

[How to manage information]

When a case is registered on the EDC, the data center automatically issues a registration number that is unrelated to the research subjects' personal information. When handling information related to this research, the registration number will be used for storage and management. In addition, a correspondence table will be created so that the research subject and the registration number can be linked. The prepared list will not be taken outside the hospital.

16 Handling of deviations from the research protocol

A protocol deviation is one in which treatment such as drug administration, ventilatory management, and surgical resection, as well as clinical tests and evaluation of toxicity and efficacy, were not performed according to the protocol provisions.

After review by the research secretariat and the research group, it will be classified into one of the following categories.

1. Violation

A “violation” is a deviation from the protocol rules that is clinically inappropriate and meets multiple of the following criteria:

(i) Affects the evaluation of the endpoints of this study.
(ii) The researcher/facility is responsible.
(iii) Intentional or systemic
(iv) The degree of danger or deviation is significant.

In principle, 'Violations' should describe the details of each violation when the paper is published.

2. Deviation

Deviations that do not qualify as "violations" or "tolerances". If many specific deviations are found, they should be described in the publication of the paper.

3. Acceptable deviation

Deviations from the protocol within acceptable limits established before or after the start of the study between the research group and the Principal Investigator/Research Office.

17 Changes to the research protocol, etc.

When changing or revising the research plan, consent document, or explanatory document for this research, permission must be obtained in advance from the head of the institution participating in the research. Until permission is obtained from the head of the institution participating in the research, the research will not be conducted with a modified research plan, nor will the revised content be explained.
18 Cost burden for research subjects
1) Burden of medical fees
All treatments and tests used in this study are approved by insurance for the treatment of pulmonary fibrosis. All medical costs, including drug costs, for study participants during the study period will be paid by the patient's usual health insurance and patient self-pay.
2) Compensation for health damage
14 Response to and Compensation for Damage to the Health of Research Subjects.

19 Registration of research plan and publication of research results
19.1 Register research plan
The research protocol will be registered in the University Hospital Medical Information Network Clinical Trial Registration System UMIN-CTR (UMIN000026376).
2) The final results of this study are to be published in an English-language journal. The presenters of the papers and conference presentations will be decided by the CJLSG Board of Directors in consideration of their contribution to this research.

19.2 Publication of research results
Upon completion of the research, the Chief Investigator shall, without delay, publish the results of said research after taking necessary measures to protect the human rights of the research subjects and their related persons or the rights and interests of the researchers and their related persons. The confidentiality of the research subjects will be protected during the publication of the results. The goal is to publish the results of this research in an English-language journal. The CJLSG Board of Directors will decide the presenters of papers and conference presentations in consideration of their contribution to this research.

19.3 Disclosure to research subjects
The head of the institution participating in the research will promptly respond to any request from the research subject or his/her representative for disclosure of personal information pertaining to the research subject, etc.

20 Attribution of research results, secondary use of research data, and publication of research results
20.1 Attribution of research results
The results obtained from this study shall belong to the CJLSG1601 Research Office. Nippon Boehringer Ingelheim Co., Ltd. will have the right to use the results. The research subjects will not have this right. The results obtained through this research will be published regardless of the outcome.

20.2 Secondary use of research data
If the CJLSG 1601 Secretariat judges that secondary use of the data obtained in this study is useful, the data may be used for secondary purposes with the consent of the Chief Investigator and the CJLSG Board of Directors, paying close attention to the protection of personal information. The procedures for such secondary use shall be in accordance with the Ethical Guidelines for Medical Research Involving Human Subjects (announced on December 22, 2014, and partially revised on February 28, 2017).

20.3 Publication of the results
When the results are published, they will be reported as a joint presentation by the research participating institutions. All conference reports and publications related to this study will be determined by the Chief Investigator and CJLSG1601 Research Office according to the contribution to the study. All co-authors should be involved in the preparation of the manuscript and agree on the content before submission. If no agreement is reached after discussion of the content, the Chief Investigator may not include the researcher as a co-author.
When submitting papers or presenting at conferences, presenters other than the CJLSG 1601 Research Office (Principal Investigator and Medical Officer) are not allowed to receive the results of tabulation and analysis without the approval of the Principal Investigator and CJLSG 1601 Research Office (Principal Investigator and Medical Officer).

21 Research funding and conflicts of interest
21.1 research funds
The funds for this study will be provided by Nippon Boehringer Ingelheim Co., Ltd. to the Central Japan Respiratory System Clinical Research Group (CJLSG), a non-profit organization, based on a contractual agreement. The CJLSG will pay the research expenses to the participating institutions using the research expenses paid by Nippon Boehringer Ingelheim Co. The funders, Nippon Boehringer Ingelheim Co., Ltd. will be involved in the conception of the study and the provision of information, but will not be involved in any way in the implementation of the plan or in the analysis and interpretation of the results.
21.2 Conflict of interest

Decisions regarding the planning, implementation, and publication of this research, as well as the analysis of the results obtained in this research, will be made by the facilities participating in the research, including the principal investigator of this research. Each researcher shall manage conflicts of interest appropriately, such as by following the conflict of interest management policies of the academic societies and institutions to which he or she belongs, and shall disclose the results of the research appropriately upon request of the academic societies and medical journals in which he or she plans to publish the research results. The research will be conducted by the research organization completely independently, without the involvement of Nippon Boehringer Ingelheim Co.

22 Monitoring and auditing

22.1 Monitoring

In principle, regular monitoring will be conducted twice a year to ensure that the research is being conducted safely and in accordance with the protocol, and that data are being collected accurately. Monitoring will be conducted centrally based on the data entered in the CRFs collected at the data center, and will not include site visits to check the data against the source documents. Periodic monitoring reports prepared by the research secretariat will be submitted to the principal investigator, the principal investigator of the research participating institution, and the efficacy and safety evaluation committee for review.

Since the purpose of periodic monitoring is to improve the scientific and ethical nature of research by providing feedback on problems and is not intended to uncover problems in research or facilities, the research secretariat, the principal investigator, and the principal investigators of the facilities participating in the research should strive to improve the problems identified in the periodic monitoring reports. In addition, the research secretariat, the principal investigator, and the principal investigators of the participating institutions will strive to improve the problems identified in the periodic monitoring reports.

Monitoring items

(i) Status of achievement of accumulation
(ii) Eligibility
(iii) Pre-treatment background factors
(iv) Whether the protocol is being treated or treatment has been terminated, and the reason for discontinuation/termination.
(v) Deviation from protocol
(vi) Serious adverse events
(vii) Adverse events
(viii) Other issues related to the progress and safety of the study.

22.2 Audit

The purpose of this study is to conduct a facility visit audit to improve the scientific and logical quality of the study. An audit organization that is not affiliated with the CILSG, the study site, the pharmaceutical company, or the data center will be designated in advance and commissioned. The institution in charge of the audit will visit the research site and check approval documents, patient consent forms, and CRF entry data against medical records (direct access to source documents) in accordance with the audit manual and standard operating procedures prepared by the institution in charge of the audit. The person in charge at the institution in charge of the audit should submit a written pledge of confidentiality to the institution prior to the audit in accordance with the rules of the institution.

For this reason, it is necessary to explain to patients and obtain their written consent prior to enrollment in the study that materials pertaining to their personal information, such as medical records, may be subject to audit when they participate in this study.

The results of the audit, together with the results of the review of the audit report, will be reported to the Institutional Review Scientist at the site, the head of the site participating in the study, the CILSG Research Secretariat and the Research Supervisor, the Data Center, the CILSG Secretariat, and the CILSG President. It will also be reported to the group investigators and the CILSG Steering Committee, as appropriate. In any other publication, the name of the institution will be withheld.

23 Attachments

Ofev attachment, Rehabilitation procedure, SGRQ Japanese version Ver2, CAT, HAD, Dyspnea-12

24 References


V. EXERCISE TRAINING PROTOCOL

1. Outpatient pulmonary rehabilitation (PR) supervised by a cardiorespiratory physiotherapist

Participants attended a twice-weekly, 12-week supervised outpatient pulmonary rehabilitation program (PRP) and completed an individually prescribed home exercise program. The supervised program consisted of 60 minutes of exercise training (endurance and resistance training). The components of the exercise training program are as follows:

1.1. Endurance training (cycling 15 min + walking 15 min)

This comprised 15 minutes each of stationary cycling and treadmill or corridor walking. Participants prescribed long-term oxygen therapy (LTOT) exercised using supplementary oxygen. Further, those not prescribed LTOT but in whom percutaneous oxygen saturation (SpO₂) was less than 85% received supplemental oxygen during exercise.

1) Cycling

The initial intensity for cycling was 80% of the peak work rate achieved on the incremental exercise test for those participants in whom the endurance time (ET) measured using a constant-load cycle ergometer test was more than 15 minutes. In those with an ET less than 15 minutes, the initial intensity for training was 60% and this was increased in increments of 10% to achieve a training intensity of 80% within 3 weeks. Interval training (cycling for 1 min at 80% of peak work rate, alternating with 1 min rest intervals) was also utilized according to the following protocol (Fig. 1) if a participant was unable to tolerate continuous exercise. Progression of training was achieved by increasing workload to the level that participants reported a dyspnea or rate of perceived exertion score of at least 3 or 4 (“moderate” to “somewhat severe”) on the modified Borg scale².

![Fig 1. cycling training protocol](image)

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2) Walking
The initial intensity for walking was 80% of the average speed achieved on the 6-minute walk test\(^3\). Participants unable to tolerate walking on the treadmill walked in a corridor. This group was told the distance to cover each minute and over the 15 min, and given an individualized target dyspnea score from the modified Borg scale\(^2\). If a participant could not tolerate 15 min or continuous walking, he or she was instructed to take rests but to achieve a total of 15 min walking. The walking intensity (speed) was progressed individually according to each participant’s ability.

1.2. Resistance training
The resistance training comprised two upper limbs and one lower limb exercise using weight bands or dumbbells. The initial load for the upper limb exercises (shoulder flexion, shoulder abduction) was 1-2 kg in each hand, and 10 repetitions were performed. This was increased by 1-2 sets until a total of 5 sets was reached. The weight was then increased by 0.5-1kg for each hand every 1 or 2 weeks. Lower limb resistance training, knee extension exercise, commenced with a load of 2 kg and 5 sets of 10 repetitions, and was increased by 1-2 kg every 1 or 2 weeks when the participant could perform the exercises without any difficulty.

1.3. Monitoring and recording during training
SpO\(_2\) was monitored during each exercise session, and maintained above 85% with oxygen administration. Participants were encouraged to rest when they perceived strong dyspnea or leg fatigue (≥ 7 on the modified Borg scale). The physiotherapist recorded dyspnea, fatigue and other symptoms, SpO\(_2\) and pulse rate, program descriptions, exercise intensity and duration for all participants for each of the exercise sessions.

1.4. Home exercise program
Participants were instructed to complete an unsupervised home exercise program on two days each week. The program comprised endurance and resistance exercises of similar intensity (at the same dyspnea or rate of perceived exertion score on the modified Borg scale) and duration of walking (endurance exercise), and the number of repetitions and sets (resistance training) as the supervised exercise sessions. Resistance training was accomplished using resistance bands or the participant’s body weight. For lower limb exercise, 3 sets of 10 hip abductions and knee extensions with resistance bands, and 3 sets of 5 squats and 10 standing calf raises each were prescribed.
Participants were also instructed to increase their physical activity and to measure daily step counts except on the days when neither supervised nor unsupervised exercise training was undertaken. The goal was to increase the daily step count by 10% each month, up to 6,000 steps per day.
These individualized programs were given to the participant in the format of exercise cards. Participants recorded exercise sessions in an exercise diary, including the type, frequency, duration and intensity of walking exercises, and the number and type of resistance exercises performed. A physiotherapist regularly reviewed the diary to determine if the exercises were performed with the same intensity, duration and number of sets, and repetition of exercises as the supervised exercises, and provided feedback.
2. Maintenance pulmonary rehabilitation

At the completion of the 12-week outpatient PRP participants underwent a 40-week maintenance program. They were instructed to complete their home exercise program at least 4 days per a week, and attended the supervised outpatient PR at least once every 4 weeks. The home exercise program was identical to that undertaken during the 12-week initial PRP. Exercise diaries and pedometers were used to encourage participants to maintain the frequency, duration and intensity of the exercise prescription, and physical activity.

Participants recorded the type, number, and duration of exercises they performed, and implementation of the exercise program was self-rated on a 5-point Likert scale (from “I couldn't do it at all” to “I could do it well”) in the home diary. Physiotherapists reviewed the exercise diary and provided feedback to the participants when attending the outpatient program.

References