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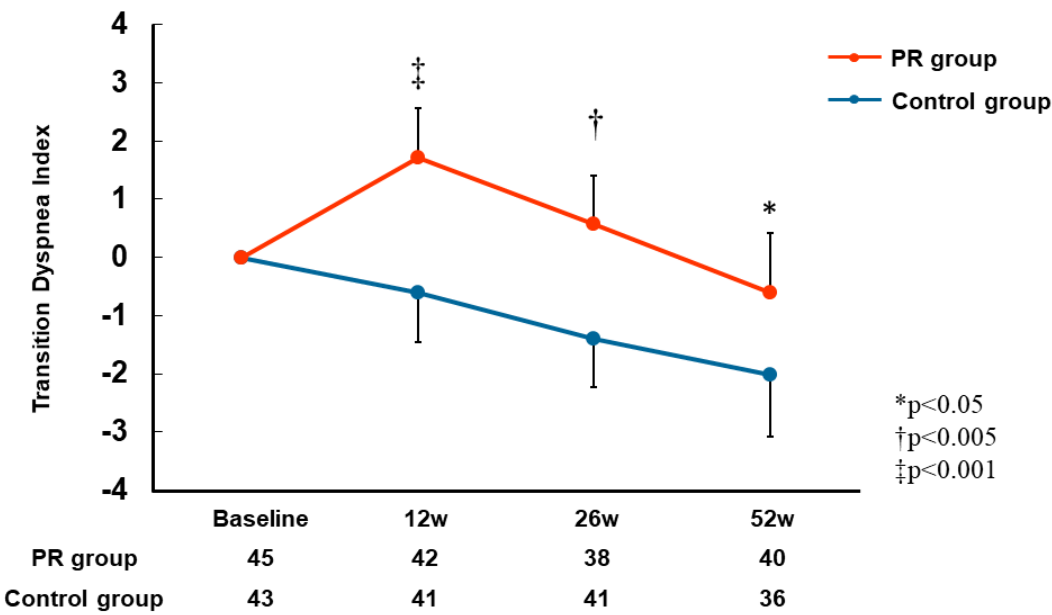
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II. List of hospitals that cooperated in the trial

Tosei General Hospital
Kindai University Faculty of Medicine
Kanagawa Cardiovascular and Respiratory Center
KKR Takamatsu Hospital
Kirigaoka Tsuda Hospital
Kobe City Medical Center General Hospital
Kobe City Medical Center West Hospital
Ogaki Municipal Hospital
Nagoya University Hospital
Nagasaki University Hospital
Saiseikai Kumamoto 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

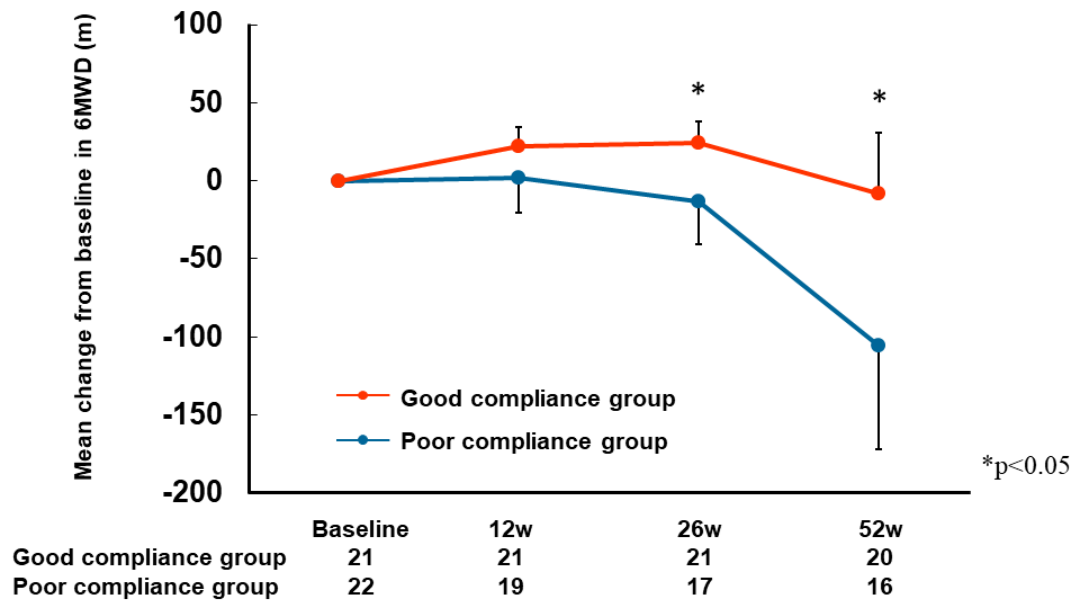
III. SUPPLEMENTARY FIGURES

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

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

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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.¹⁾ 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 weeks²⁻⁴⁾. 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 IPF⁵⁾. 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^{6,7)}. 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^{8,9)}. 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.

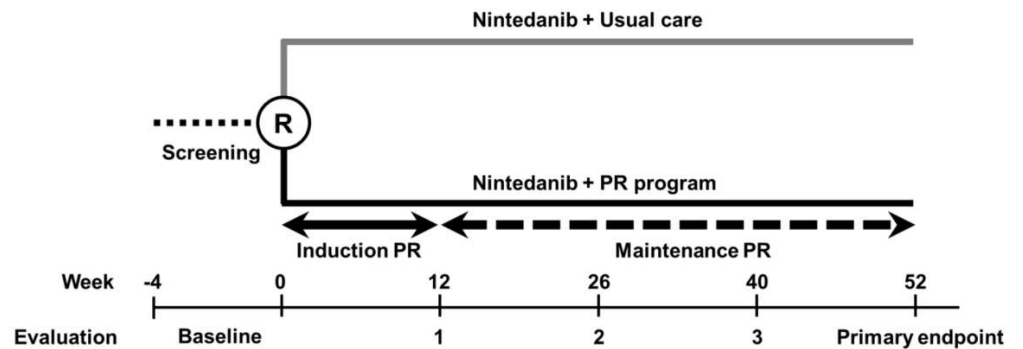
3 Objectives

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
- Invasion: 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
The duration of treatment will be 52 weeks for both groups.



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4.3 Study drug

[Nintedanib]

Research drug name	Ofev 150mg soft capsules Ofev 100mg soft capsules
Manufactured by	Nippon Boehringer Ingelheim Co.
Drug information	https://www.info.pmda.go.jp/go/pack/3999039M1022_1_10/

[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) Dyspnoea on exertion (modified Medical Research Council scale 1-3) (see 4.4.2).
- 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 for four weeks before enrolment 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) $\geq 50\%$, $79\% \geq$ % diffusing capacity for carbon monoxide (DLCO) $\geq 30\%$, and forced expiratory volume in the first second (FEV1)/FVC $\geq 70\%$ 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 ¹⁰⁾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.

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- 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 = $(140 - \text{age}) \times \text{weight (kg)} \times 0.85$ (for women) / $(72 \times \text{serum creatinine (mg/dL)})$

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 results of the 6-minute walk test, which is the primary endpoint, are strongly affected by conditions other than IPF, and the effect of PR 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 it 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 C or 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 dyspnoea on exertion Modified Medical Research Council (mMRC) grade

grade	Degree of the breathlessness related to activities
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on the level or walking up a slight hill.
2	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.


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3	I stop for breath after walking about 100 m or after a few minutes on the level.
4	I am too breathlessness to leave the house or I am breathless when dressing or undressing.

4.5 Study period
Date of approval by the director of each joint research facility - April 30, 2021 (Registration deadline: December 31, 2019)

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4.6 Summary of protocol visit and assessments

Evaluation	Inclusion	Baseline -4w				
			12w±14d	26w±14d	40w±14d	52w (50w-56w)
consent acquisition	•	•	•	•	•	•
patient background	•	•	•	•	•	•
HRCT confirmed within 12 months	•	•	•	•	•	•
arterial blood gas	•	•	•	•	•	•
Resting SpO ₂	•	•	•	•	•	•
6MWT	•	•	•	•	•	•
Exercise duration	•	•	•	•	•	•
Respiratory function test (FVC)	Within 1 month	•	•	•	•	•
Respiratory function test (DLco)	Within 1 month	•	•	•	•	•
Health status (SGRQ, CAT)	•	•	•	•	•	•
Anxiety and Depression (HADS)	•	•	•	•	•	•
modified MRC	•	•	•	•	•	•
dyspnea (BDI/TDI, Dyspnea-12)	•	•	•	•	•	•
Physical activity (number of steps)	•	•	•	•	•	•
ECG	•	•	•	•	•	•
blood chemistry test	•	•	•	•	•	•
Nintedanib medication status	•	during the study period				
Rehabilitation diary (Group B only)	•	during the study period				
LTOT status	•	during the study period				
adverse event	•	at any time				
unscheduled hospitalization	•	at any time				

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.

Evaluation point	From the test introduction	Allowances
Baseline evaluation		Minus 28 days - allocation
Mid-term evaluation	12 weeks, 26 weeks, 40 weeks	Minus 14 days to plus 14 days
Final evaluation	52 weeks	Minus 14 days to plus 28 days

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".

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 (INPULSIS 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 SpO after

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examination 2

- 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, γ GTP, LDH, CRP, KL-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

Pirfenidone (If pirfenidone 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 Concomitantly 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 pirfenidone, 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 disuse, 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.

Precautions 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.

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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.

Evaluation point	From the test introduction	Allowances
Baseline evaluation		Minus 28 days - allocation
Mid-term evaluation	12 weeks, 26 weeks, 40 weeks	Minus 14 days to plus 14 days
Final evaluation	52 weeks	Minus 14 days to plus 28 days

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 quality level of evidence for the treatment of chronic stable IPF. The quality of the evidence level for recommendations/discommendations 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 first be 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 ($>/\leq 350$ m), (2) institution, (3) %FVC within 1 month before enrollment ($>/\leq 70\%$)

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.

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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 ($>/\leq 350$ m), (2) facility, and (3) %FVC ($>/\leq 70\%$) 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 ($>/\leq 350$ m)

(2) Facilities

(iii) %FVC within 1 month prior to registration ($>/\leq 70\%$)

[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 enrollment 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 ($\geq 70\%$, $70\%>$) 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 missing 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/SHIRYOU/ctcae.htm>). 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

[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⁾Dowman 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 study¹²⁾. 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 bicycle 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
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	criteria
Safety analysis	Patients enrolled in the study who received at least one dose of the test treatment
Full Analysis Set; FAS	Patients enrolled in the study who received at least one dose of the test treatment
Per Protocol Set; PPS	A population from which FAS excluded cases that were in conflict with Cases that were found to be ineligible after registration Cases that violate the study protocol that may affect the efficacy evaluation Cases in which the efficacy cannot be sufficiently evaluated due to inadequate observation

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, midterm assessment-1, midterm assessment-2, midterm 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, midterm assessment-1, midterm assessment-2, midterm 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.

(3) Methods: Repeated measures mixed effects model (MMRM) will be used for the analysis. The interaction terms between the 6MWD, the treatment group, the study time point, and the treatment group and the study time point at the baseline assessment will be fixed effects, and the change in the 6MWD 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.

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.

(3) Methods of evaluation: Repeated measures mixed effects model (MMRM) will be used for analysis. The

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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 compared 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

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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 | 12. provision of test results |
| 2. you are free to participate in clinical research | 13. protection of personal information |
| 3. about the disease of which this study is a part | 14. handling of information obtained from the research |
| 4. the purpose of the research | 15. response and compensation in the event of health damage |
| 5. the nature of the research | 16. cost sharing |
| 6. other treatment methods | 17. conflicts of interest and sources of funding for research |
| 7. expected duration of the study and number of participants | 18. attribution of intellectual property rights |
| 8. expected benefits and disadvantages | 19. the organization of this research |
| 9. what you must observe | 20. inquiries and contact information |
| 10. the case of discontinuation of the research | 21. consultation service for opinions and complaints |
| 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 PR, 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

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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

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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 subject's 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 subject's 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 systematic

(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.

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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 CJLSG, 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 Research Scientist at the site, the head of the site participating in the study, the CJLSG Research Secretariat and the Research Supervisor, the Data Center, the CJLSG Secretariat, and the CJLSG President. It will also be reported to the group investigators and the CJLSG 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

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- 4) Dowman L, et al. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev* Issue 10: 2014.
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- 8) Richeldi L, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071-2082.
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- 11) Dowman L, et al. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev*. 2014 Oct 6;(10).
- 12) Ryerson CJ, et al. High oxygen delivery to preserve exercise capacity in patients with Idiopathic pulmonary fibrosis treated with nintedanib. *Methodology of the HOPE-IPF Study*. *Ann Am Thorac Soc*. 2016;13(9):1640-1647.

V. EXERCISE TRAINING PROTOCOL

1. Outpatient pulmonary rehabilitation (PR) supervised by a cardiorespiratory physiotherapist¹

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.

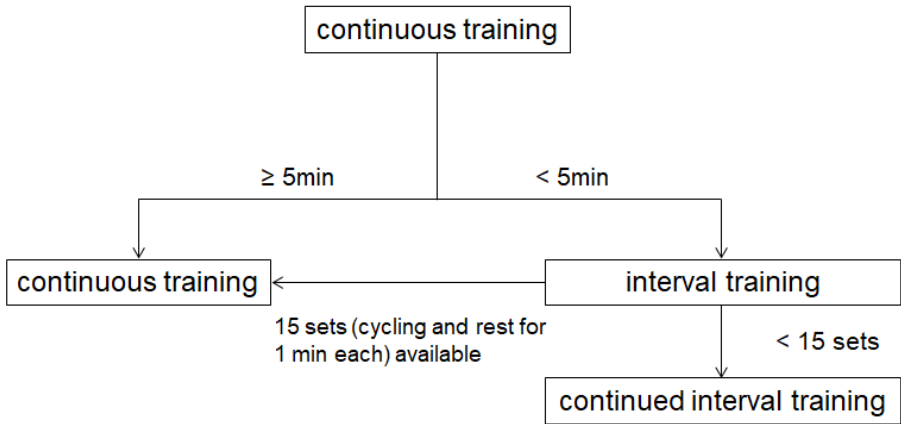


Fig 1. cycling training protocol

2) Walking

The initial intensity for walking was 80% of the average speed achieved on the 6-minute walk test³. 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 scale². 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

SpO₂ 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, SpO₂ 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 rehabilitation¹

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

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2. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc.* 1982;14(5):377-381.
3. Jenkins S, Hill K, Cecins NM. State of the art: how to set up a pulmonary rehabilitation program. *Respirology.* 2010;15(8):1157-1173.