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Optimizing Antifibrotic Therapy with Low-Dose Pirfenidone Plus Nintedanib versus High-Dose Pirfenidone or Nintedanib Monotherapy in Idiopathic Pulmonary Fibrosis (OPTIMA-IPF Study): A 36-Month Single-Centre Comparative Study

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Abstract

Background

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease associated with relentless decline in lung function, impaired quality of life, and high mortality despite currently available antifibrotic therapies. Although pirfenidone and nintedanib slow disease progression, tolerability issues, particularly gastrointestinal adverse effects with high-dose pirfenidone, frequently limit treatment adherence. The OPTIMA-IPF (Optimizing Antifibrotic Therapy in Idiopathic Pulmonary Fibrosis) Study evaluated whether combining low-dose pirfenidone with nintedanib provides superior long-term clinical efficacy and tolerability compared with high-dose pirfenidone or nintedanib monotherapy.

Methods

The OPTIMA-IPF Study was a prospective, randomized, single-centre comparative study with 36 months of follow-up (Institutional Review Board approval VCC:012/2022). Eighty-four patients with IPF diagnosed according to ATS/ERS clinical-radiological criteria were equally allocated to three treatment groups (n = 28 each): high-dose pirfenidone (1,800–2,400 mg/day according to tolerance), nintedanib (100 mg three times daily), or combination therapy comprising nintedanib (100 mg three times daily) plus low-dose pirfenidone (400 mg three times daily). All participants had baseline forced vital capacity (FVC) > 50% predicted and received standard supportive care, including influenza and pneumococcal vaccination. Clinical assessment was performed monthly, pulmonary function testing every six months, and high-resolution computed tomography annually. Primary analyses compared exercise capacity, pulmonary function, radiological progression, exacerbation frequency, adverse events, and mortality after 36 months using chi-square, one-way ANOVA, and paired *t*-tests.

Results

The combination therapy group demonstrated significantly greater preservation of exercise capacity, with superior 6-minute walk distance and faster recovery of heart rate and oxygen saturation compared with both monotherapy groups ($p = 0.0017$ and $p = 0.0038$, respectively). Radiological progression was significantly reduced, with fewer patients demonstrating worsening fibrosis, central extension of disease, and extensive reticulation or honeycombing ($p = 0.0019$, $p = 0.0060$, and $p = 0.0012$, respectively). Lung function outcomes also differed significantly among treatment groups, with combination therapy achieving the highest proportion of patients with stable or improved FVC and the lowest proportion experiencing > 10% FVC decline ($p = 0.0089$). Annual exacerbation rates requiring hospitalization were significantly lower in the combination group ($p = 0.0004$). High-dose pirfenidone was associated with significantly greater nausea, vomiting, weight loss, anorexia, and treatment intolerance, whereas gastrointestinal adverse events were substantially less frequent with combination therapy and

nintedanib alone. During follow-up, disease-related mortality occurred in five patients receiving pirfenidone and three patients each receiving nintedanib monotherapy and combination therapy.

Conclusions

The OPTIMA-IPF Study demonstrates that combining low-dose pirfenidone with nintedanib provides clinically meaningful long-term benefits over high-dose pirfenidone and offers incremental advantages over nintedanib monotherapy by improving functional capacity, preserving lung function, reducing radiological progression and exacerbation risk, while maintaining superior gastrointestinal tolerability. These findings suggest that low-dose pirfenidone may serve as an effective adjunct to nintedanib, improving treatment adherence and potentially optimizing long-term outcomes in patients with idiopathic pulmonary fibrosis.

Research Highlights

1. First 36-month prospective comparative study evaluating low-dose pirfenidone (400 mg three times daily) plus nintedanib (100 mg three times daily) against high-dose pirfenidone and nintedanib monotherapy in 84 patients with idiopathic pulmonary fibrosis.
2. Combination therapy achieved the best functional outcomes, with 19/28 (67.9%) patients walking >450 m on the 6-minute walk test compared with 17/28 (60.7%) receiving nintedanib and 5/28 (17.9%) receiving pirfenidone (p=0.0018).
3. Radiological disease stabilization (<10% HRCT progression) was observed in 22/28 (78.6%) patients receiving combination therapy compared with 20/28 (71.4%) receiving nintedanib and 10/28 (35.7%) receiving pirfenidone (p=0.0019).
4. Preservation of lung function was greatest with combination therapy, with 22/28 (78.6%) patients demonstrating <10% FVC decline, compared with 21/28 (75.0%) receiving nintedanib and 12/28 (42.9%) receiving pirfenidone (p=0.0089).
5. Exacerbation-related hospitalizations were lowest with combination therapy, with 24/28 (85.7%) patients requiring 0–1 hospitalization/year, compared with 19/28 (67.9%) receiving nintedanib and 10/28 (35.7%) receiving pirfenidone (p=0.0004).
6. Low-dose pirfenidone plus nintedanib markedly improved gastrointestinal tolerability, reducing nausea/vomiting and anorexia to 2/28 (7.1%) compared with 20/28 (71.4%) with high-dose pirfenidone, while disease-related mortality remained lower (3 vs. 5 deaths) over the 36-month follow-up.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause characterized by irreversible loss of lung function, worsening respiratory symptoms, impaired

quality of life, and premature mortality. It predominantly affects older adults and is radiologically and histopathologically characterized by a usual interstitial pneumonia (UIP) pattern. Despite advances in diagnosis and management, the median survival following diagnosis remains only 3–5 years, making IPF one of the most lethal chronic respiratory diseases worldwide. Disease progression is highly heterogeneous, with many patients experiencing gradual decline interrupted by acute exacerbations that substantially increase mortality risk and healthcare utilization. [1–3]

Current international ATS/ERS/JRS/ALAT guidelines recommend antifibrotic therapy with pirfenidone or nintedanib for patients with IPF because both agents slow the decline in forced vital capacity (FVC), reduce disease progression, and may improve long-term survival. However, neither drug reverses established fibrosis, restores lung function, nor completely prevents disease progression or acute exacerbations. Consequently, there remains an unmet need for therapeutic strategies that further improve long-term clinical outcomes while maintaining acceptable tolerability. [1, 4]

Pirfenidone is an orally administered antifibrotic agent with anti-inflammatory, antioxidant, and transforming growth factor-β (TGF-β)-modulating properties. Clinical trials, including the CAPACITY and ASCEND studies, demonstrated significant reductions in annual FVC decline and progression-free survival compared with placebo. Nevertheless, gastrointestinal intolerance, anorexia, nausea, vomiting, photosensitivity, fatigue, and weight loss frequently limit treatment adherence, particularly when full therapeutic doses (1800–2403 mg/day) are required for prolonged periods. [5–7]

Nintedanib is an intracellular tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) receptors, thereby inhibiting fibroblast proliferation and extracellular matrix deposition. The INPULSIS trials established that nintedanib significantly slows annual FVC decline across a broad spectrum of patients with IPF and has become one of the standard antifibrotic therapies worldwide. Diarrhoea remains the most frequently reported adverse event but is generally manageable with dose adjustment and supportive treatment. [8–10]

Because pirfenidone and nintedanib exert antifibrotic effects through complementary molecular pathways, combination therapy has attracted increasing interest as a strategy to maximize disease stabilization while minimizing toxicity. Several early-phase studies, including INJOURNEY and other observational investigations, have demonstrated that concomitant administration of pirfenidone and nintedanib is feasible and generally well tolerated, although gastrointestinal adverse effects remain a concern and robust long-term comparative data are lacking. Most published studies have evaluated standard-dose combinations over relatively short follow-up periods and have not specifically assessed whether reducing the pirfenidone dose while maintaining nintedanib therapy can preserve efficacy with improved tolerability. [11–14]

In routine clinical practice, many patients are unable to tolerate full-dose pirfenidone because of persistent gastrointestinal adverse effects, anorexia, and progressive weight loss, often resulting in dose

reduction or treatment discontinuation. Whether the addition of low-dose pirfenidone to nintedanib provides additive antifibrotic benefits while minimizing adverse events has not been adequately investigated, particularly in long-term prospective comparative studies. The OPTIMA-IPF (Optimizing Antifibrotic Therapy in Idiopathic Pulmonary Fibrosis) Study was therefore designed to compare high-dose pirfenidone, nintedanib monotherapy, and combination therapy comprising nintedanib with low-dose pirfenidone over a 36-month follow-up. We hypothesized that combination therapy would provide superior preservation of lung function, better exercise performance, reduced radiological progression, fewer exacerbation-related hospitalizations, and improved gastrointestinal tolerability compared with conventional high-dose pirfenidone or nintedanib monotherapy.

Methods

Study Design and Setting

The OPTIMA-IPF (Optimizing Antifibrotic Therapy in Idiopathic Pulmonary Fibrosis) Study was a prospective, randomized, single-centre, comparative study conducted at Venkatesh Chest Hospital and Critical Care Center, Latur, Maharashtra, India, between January 2022 and December 2025. The study evaluated the long-term efficacy and safety of low-dose pirfenidone combined with nintedanib compared with high-dose pirfenidone or nintedanib monotherapy in patients with idiopathic pulmonary fibrosis (IPF). The study protocol was approved by the Institutional Review Board and Institutional Ethics Committee (Approval No. VCC:012/2022), and written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) principles, and reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies.

Study Population

A total of 84 consecutive patients with newly diagnosed or previously untreated IPF were enrolled after screening according to predefined eligibility criteria. Diagnosis of IPF was established according to the 2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline, based on multidisciplinary discussion integrating clinical presentation, high-resolution computed tomography (HRCT), and histopathological findings when required. Only patients with baseline forced vital capacity (FVC) > 50% predicted were included to ensure comparable disease severity at study entry.

Inclusion Criteria: Patients were eligible if they fulfilled all of the following criteria:

1. Age ≥ 40 years.
2. Diagnosis of idiopathic pulmonary fibrosis according to ATS/ERS/JRS/ALAT criteria.
3. HRCT demonstrating definite or probable usual interstitial pneumonia (UIP) pattern, or multidisciplinary diagnosis of IPF.

4. Baseline FVC > 50% predicted.
5. Ability to perform pulmonary function testing and 6-minute walk test.
6. Ability to provide written informed consent.
7. Willingness to complete the scheduled 36-month follow-up.

Exclusion Criteria: Patients were excluded if they had any of the following:

1. Interstitial lung disease secondary to connective tissue disease, occupational exposure, hypersensitivity pneumonitis, or drug toxicity.
2. Active pulmonary tuberculosis or active respiratory infection.
3. Significant hepatic impairment (transaminases > 3× upper limit of normal).
4. Severe renal dysfunction.
5. Active malignancy with life expectancy < 1 year.
6. Pregnancy or lactation.
7. Contraindication or hypersensitivity to pirfenidone or nintedanib.
8. Inability to complete scheduled follow-up.

Randomization and Treatment Allocation

Following enrolment, patients were equally allocated into three treatment groups (n = 28 each):

- Group A (High-dose Pirfenidone): Pirfenidone 1800–2400 mg/day, adjusted according to individual tolerability.
- Group B (Nintedanib): Nintedanib 100 mg three times daily throughout the study period.
- Group C (Combination Therapy): Nintedanib 100 mg three times daily plus low-dose pirfenidone 400 mg three times daily.

Dose modifications were permitted for adverse events while maintaining treatment whenever clinically feasible.

Standard Supportive Care

All participants received identical background management, including annual influenza vaccination, pneumococcal vaccination, smoking cessation counselling when appropriate, pulmonary rehabilitation advice, nutritional counselling, supplemental oxygen when indicated, management of gastro-oesophageal reflux disease and other comorbidities, and routine supportive therapy according to contemporary international IPF management recommendations.

Follow-up and Outcome Assessment

Patients were followed for 36 months with scheduled assessments throughout the study period. Clinical evaluations were performed monthly, documenting symptoms, dyspnoea, adverse events, treatment adherence, exacerbations, hospitalization, body weight, and survival. Pulmonary function testing was performed every six months, including spirometry according to ATS/ERS standards. The primary physiological outcome was annual change in forced vital capacity (FVC), categorized as:

- 10% decline
- < 10% decline (stable disease)

Exercise performance was assessed every six months using the 6-minute walk test (6MWT). Walking distance, exercise-induced oxygen desaturation, heart-rate response, and recovery time required for normalization of oxygen saturation and heart rate were recorded.

HRCT thorax was performed at baseline and annually. Radiological assessment included:

- progression of fibrosis grade,
- disease stability (< 10% radiological progression),
- central versus peripheral extension of fibrosis,
- progression of reticulations,
- progression of honeycombing.

Acute exacerbations were prospectively documented throughout follow-up, including hospitalization frequency and disease-related mortality.

Safety assessments included gastrointestinal intolerance (nausea, vomiting, anorexia), diarrhoea, weight loss, cardiovascular adverse events, liver dysfunction, and treatment discontinuation.

Study Outcomes

Primary Outcomes

- Annual decline in FVC.
- Exercise performance assessed by 6-minute walk distance.
- HRCT progression of pulmonary fibrosis.
- Exacerbation-related hospitalization during 36 months.

Secondary Outcomes

- Recovery following exercise-induced desaturation.

- Radiological stability.
- Treatment-related adverse events.
- Disease-related mortality.
- Overall treatment tolerability.

Rationale for Combination Therapy

The rationale for combining low-dose pirfenidone with nintedanib was based on the complementary mechanisms of action of the two antifibrotic agents and the need to improve long-term treatment tolerability. Pirfenidone suppresses profibrotic cytokines, particularly transforming growth factor-β (TGF-β), while nintedanib inhibits multiple receptor tyrosine kinases involved in fibroblast activation, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) receptors. The use of both agents may therefore provide additive inhibition of fibrogenic pathways, potentially resulting in greater preservation of lung function and reduced disease progression than either agent alone.

In routine clinical practice, however, full-dose pirfenidone (1800–2400 mg/day) is frequently associated with gastrointestinal adverse effects, including nausea, vomiting, anorexia, early satiety, and progressive weight loss, which often lead to poor treatment adherence, dose reduction, or discontinuation. Persistent anorexia and weight loss may further contribute to drug-related cachexia, an important clinical concern in patients with idiopathic pulmonary fibrosis, particularly during long-term therapy. Therefore, in the present study, low-dose pirfenidone (400 mg three times daily) was intentionally combined with nintedanib (100 mg three times daily) with the objective of maintaining complementary antifibrotic activity while minimizing pirfenidone-induced gastrointestinal toxicity, reducing the risk of anorexia and cachexia, improving treatment adherence, and enhancing long-term tolerability. We hypothesized that this strategy would preserve the clinical benefits of dual antifibrotic therapy while overcoming one of the major limitations associated with conventional high-dose pirfenidone treatment. This rationale formed the basis of the OPTIMA-IPF Study.

Case Definitions and Outcome Measures

Clinical Response

Clinical response was assessed using exercise capacity, post-exercise cardiopulmonary recovery, exacerbation frequency, hospitalization, treatment tolerability, and survival. Patients achieving a 6-minute walk distance (6MWD) > 450 m, recovery of heart rate and oxygen saturation within 1 minute, and ≤ 1 exacerbation requiring hospitalization per year were considered to have a favorable clinical response. An intermediate response was defined by a 6MWD of 150–450 m and recovery within 1–5 minutes, whereas a poor clinical response was characterized by a 6MWD < 150 m, recovery time > 5 minutes, recurrent exacerbations requiring > 1 hospitalization annually, progressive symptom deterioration, or disease-related mortality.

Spirometric Response

Pulmonary function testing was performed according to ATS/ERS recommendations at baseline and every six months. Treatment response was categorized according to the annual change in forced vital capacity (FVC). Disease stability was defined as an FVC decline of < 10% predicted, whereas disease progression was defined as an FVC decline > 10% predicted from baseline. Improvement in lung function was considered when there was a > 10% increase in FVC, although this outcome was uncommon in the present study.

Radiological Response

High-resolution computed tomography (HRCT) of the thorax was performed at baseline and annually to evaluate disease progression. Radiological stability was defined as < 10% progression in overall fibrotic involvement with preservation of the baseline fibrosis grade and predominantly peripheral or mid-zone disease distribution. Radiological progression was defined by worsening HRCT fibrosis grading, development of new central lung involvement, or an increase in the extent of reticulations and honeycombing involving > 50% of the fibrotic lung. Patients with < 50% honeycombing relative to reticulations were considered to have relatively stable fibrotic disease.

Exacerbation and Safety Assessment: Acute exacerbations were prospectively recorded throughout the 36-month follow-up. Patients requiring 0–1 hospitalization per year were classified as having a low exacerbation burden, whereas those requiring > 1 hospitalization annually were considered to have frequent exacerbations. Safety evaluation included treatment-related gastrointestinal adverse events (nausea, vomiting, anorexia, diarrhoea), weight loss, cardiovascular events, and liver dysfunction. Particular emphasis was placed on pirfenidone-induced anorexia and weight loss, as these may contribute to drug-related cachexia during prolonged therapy. The use of low-dose pirfenidone in combination with nintedanib was therefore intended to preserve complementary antifibrotic efficacy while improving gastrointestinal tolerability, reducing the risk of anorexia and cachexia, and enhancing long-term treatment adherence.

Methodology

The overall methodology of the OPTIMA-IPF Study is summarized in Fig. 1. Briefly, this was a prospective, randomized, single-centre comparative study conducted in adults with idiopathic pulmonary fibrosis (IPF) diagnosed according to the 2022 ATS/ERS/JRS/ALAT criteria. Following eligibility screening and written informed consent, 84 patients were equally allocated to receive high-dose pirfenidone (1800–2400 mg/day), nintedanib monotherapy (100 mg three times daily), or combination therapy comprising nintedanib (100 mg three times daily) plus low-dose pirfenidone (400 mg three times daily). Low-dose pirfenidone was selected to reduce gastrointestinal intolerance, anorexia, weight loss, and drug-related cachexia while preserving complementary antifibrotic efficacy with nintedanib. All patients received standard supportive care and were followed for 36 months with monthly clinical assessments, spirometry and 6-minute walk testing every six months, and annual HRCT thorax. Clinical

response was assessed using 6-minute walk distance (6MWD), recovery following exercise, exacerbation frequency, hospitalization, and mortality, while spirometric and radiological responses were evaluated using annual FVC decline and HRCT progression of fibrosis, respectively. Treatment-related adverse events and overall tolerability were prospectively recorded throughout follow-up. The complete study workflow is illustrated in Fig. 1.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Normality of continuous variables was assessed using the Shapiro–Wilk test. Between-group comparisons of continuous variables were performed using one-way analysis of variance (ANOVA) with appropriate post hoc analysis when statistically significant. Paired comparisons between baseline and follow-up measurements within each treatment group were analysed using the paired Student's t-test. Categorical variables, including exercise performance, HRCT progression, FVC decline categories, hospitalization frequency, adverse events, and mortality, were analysed using the Pearson chi-square (χ^2) test or Fisher's exact test when expected cell

Results

In the present study, the baseline demographic and clinical characteristics were comparable across the three treatment groups. The majority of patients were aged 60–80 years, accounting for 16/28 patients in the pirfenidone group, 15/28 in the nintedanib group, and 12/28 in the combination therapy group, while the remaining patients were aged 40–60 years. Males slightly predominated in all groups (15–16 patients per group). A history of smoking was common, being present in 17/28, 14/28, and 18/28 patients in the pirfenidone, nintedanib, and combination groups, respectively. Similarly, gastro-oesophageal reflux disease (GERD) was reported in approximately half of the patients (15–16 patients per group). Most participants experienced a diagnostic delay of more than two years from symptom onset (16/28, 15/28, and 16/28, respectively), indicating that delayed diagnosis was a frequent feature of the study population. Overall, the three treatment groups were well matched with respect to baseline demographic and clinical characteristics, providing a balanced population for subsequent comparison of treatment outcomes. [Table 1]

In the present study, significant differences were observed in exercise performance and post-exercise recovery among the three treatment groups. A walking distance > 450 m was achieved by 19/28 patients receiving pirfenidone plus nintedanib, compared with 17/28 receiving nintedanib and 5/28 receiving pirfenidone, whereas a walking distance < 150 m was most frequent in the pirfenidone group (12/28 vs. 6/28 and 3/28, respectively). This association was statistically significant (Pearson $\chi^2 = 17.21$, $p = 0.0018$; Cramer's $V = 0.39$), indicating a moderate effect size. Similarly, recovery from exercise-induced tachycardia and oxygen desaturation within 1 minute was observed in 20/28 patients receiving combination therapy, compared with 14/28 receiving nintedanib and 8/28 receiving pirfenidone, while recovery taking > 5 minutes occurred in 12/28, 4/28, and 2/28 patients, respectively. This association

was also statistically significant (Pearson $\chi^2 = 15.48$, $p = 0.0038$; Cramer's V = 0.37), demonstrating a moderate association between treatment strategy and post-exercise cardiopulmonary recovery. [Table 2]

In the present study, significant differences in radiological disease progression on HRCT thorax were observed among the three treatment groups after 36 months. Worsening of HRCT grading occurred in 18/28 patients receiving pirfenidone compared with 8/28 receiving nintedanib and 6/28 receiving combination therapy, while radiological stability (< 10% change) was achieved in 22/28 patients in the combination group, 20/28 in the nintedanib group, and 10/28 in the pirfenidone group (Pearson $\chi^2 = 12.52$, $p = 0.0019$; Cramer's V = 0.39). Similarly, new central lung involvement was more frequent with pirfenidone (16/28) than with nintedanib (8/28) and combination therapy (5/28), whereas disease remained predominantly peripheral/mid-zone in 23/28, 20/28, and 12/28 patients, respectively (Pearson $\chi^2 = 10.22$, $p = 0.0060$; Cramer's V = 0.35). Progression to reticulations and honeycombing involving > 50% of the lung was also highest in the pirfenidone group (20/28) compared with the nintedanib (10/28) and combination (7/28) groups, while involvement < 50% was observed in 21/28, 18/28, and 8/28 patients, respectively (Pearson $\chi^2 = 13.43$, $p = 0.0012$; Cramer's V = 0.40). These findings indicate a moderate association between treatment strategy and radiological disease progression, with combination therapy demonstrating the greatest radiological stability. [Table 3]

In the present study, annual decline in FVC differed significantly among the three treatment groups. A decline of > 10% was observed in 16/28 patients receiving pirfenidone, compared with 7/28 receiving nintedanib and 6/28 receiving combination therapy. Conversely, preservation of lung function with < 10% FVC decline was achieved in 22/28 patients receiving pirfenidone plus nintedanib, 21/28 receiving nintedanib, and 12/28 receiving pirfenidone. This association was statistically significant (Pearson $\chi^2 = 13.54$, $p = 0.0089$; Cramer's V = 0.40), indicating a moderate association between treatment strategy and preservation of lung function over the 36-month follow-up period. [Table 4]

In the present study, hospitalization due to disease exacerbations during the 36-month follow-up differed significantly among the three treatment groups. 0–1 hospitalization per year was observed in 24/28 patients receiving pirfenidone plus nintedanib, compared with 19/28 receiving nintedanib and 10/28 receiving pirfenidone. In contrast, > 1 hospitalization per year occurred most frequently in the pirfenidone group (18/28), compared with 9/28 in the nintedanib group and 4/28 in the combination therapy group. This association was statistically significant (Pearson $\chi^2 = 15.44$, $p = 0.0004$; Cramer's V = 0.43), indicating a moderate-to-strong association between treatment strategy and reduction in exacerbation-related hospitalizations over 36 months. [Table 5]

In the present study, the adverse event profile differed across the three treatment groups. Nausea/vomiting and anorexia were most frequently observed in the pirfenidone group (20/28; 71.4%), compared with 4/28 (14.3%) in the nintedanib group and 2/28 (7.1%) in the combination therapy group. Similarly, weight loss occurred predominantly with pirfenidone (16/28; 57.1%) compared with 3/28 (10.7%) in both the nintedanib and combination groups. In contrast, diarrhoea was more common with nintedanib (11/28; 39.3%) than with combination therapy (6/28; 21.4%) or pirfenidone (3/28; 10.7%).

Cardiovascular adverse events were infrequent, occurring in 1/28, 3/28, and 1/28 patients, respectively, while liver dysfunction was reported in 5/28 (17.9%), 2/28 (7.1%), and 2/28 (7.1%) patients, respectively. Overall, the combination of low-dose pirfenidone plus nintedanib demonstrated the most favorable gastrointestinal tolerability while maintaining a safety profile comparable to nintedanib monotherapy. [Table 6]

Table 1
Baseline Demographic Characteristics of the Study Population

Covariates	**Pirfenidone (n = 28)**	**Nintedanib (n = 28)**	**Pirfenidone plus Nintedanib (n = 28)**
Age 40–60	12	13	16
Age 60–80	16	15	12
Females	13	12	12
Males	15	16	16
Smokers	17	14	18
Non-smokers	11	14	10
History of GERD Present	16	15	15
GERD absent	12	13	13
Diagnostic delay from symptoms > 2 years	16	15	16
Diagnostic delay from symptoms < 2 years	12	12	12

Table 2
Exercise performance tachycardia desaturation and time required for stability of saturation and heart rate

Characteristic	Pirfenidone (n = 28)	Nintedanib (n = 28)	Pirfenidone plus Nintedanib (n = 28)	Statistical analysis
Walk distance < 150 metres	12	6	3	$\chi^2 = 17.21$, $p < 0.0018$; Cramer's V = 0.39
Walk distance 150–450 metres	11	5	6	
Walk distance > 450 metres	5	17	19	
Tachycardia & desaturation recovery time 1 min	8	14	20	$\chi^2 = 15.48$, $p < 0.0038$, Cramer's V = 0.37
Tachycardia & desaturation recovery time min 1–5 min	8	10	6	
Tachycardia & desaturation recovery time > 5 min	12	4	2	

Table 3
Disease progression on HRCT thorax-grading, involvement, stability or new developments as increase in reticulations and honeycombing

Characteristic	Pirfenidone (n = 28)	Nintedanib (n = 28)	Pirfenidone plus Nintedanib(n = 28)	Statistical analysis
Worsening of grading	18	8	6	$\chi^2 = 12.52$ $p < 0.0019$; Cramer's V = 0.39
Stability (< 10% change)	10	20	22	
Involvement of central portion (new change)	16	8	5	$\chi^2 = 10.216$, $p < 0.0060$ Cramer's V = 0.35
Predominant peripheral and midzone (new change)	12	20	23	
Reticulations and honeycombing increased > 50% of total capacity	20	10	7	$\chi^2 = 13.428$ $p < 0.00121$ Cramer's V = 0.40
< 50% honeycombing than reticulations	8	18	21	

Table 4
Annual baseline FVC decline all study cases

Drug	FVC > 10% decline	FVC < 10% decline	Statistics
Pirfenidone (n = 28)	16	**12**	χ^2 =13.54
Nintedanib (n = 28)	7	**21**	p < 0.0089
Pirfenidone plus Nintedanib (n = 28)	6	**22**	Cramer's V = 0.40

Table 5
Hospitalizations due to exacerbations in 36-month follow-up

Drug group	0–1 per year require hospitalization	> 1 per year required hospitalization	Statistics
Pirfenidone (n = 28)	10	18	χ^2 =15.44
Nintedanib (n = 28)	19	9	p < 0.00044
Pirfenidone plus Nintedanib (n = 28)	24	4	

Table 6
Side effects observed during study period

Adverse event	Pirfenidone (n = 28)	Nintedanib (n = 28)	Pirfenidone plus Nintedanib (n = 28)	Total (n = 84)
Nausea/vomiting and anorexia	20 (71.4%)	4 (14.3%)	2 (7.1%)	26 (31.0%)
Weight loss	16 (57.1%)	3 (10.7%)	3 (10.7%)	22 (26.2%)
Diarrhoea	3 (10.7%)	11 (39.3%)	6 (21.4%)	20 (23.8%)
Cardiovascular adverse events	1 (3.6%)	3 (10.7%)	1 (3.6%)	5 (6.0%)
Liver dysfunction	5 (17.9%)	2 (7.1%)	2 (7.1%)	9 (10.7%)

DISCUSSION

Idiopathic pulmonary fibrosis (IPF) remains one of the most challenging chronic interstitial lung diseases because of its relentless progression, progressive functional impairment, frequent acute exacerbations, and high mortality despite the availability of antifibrotic therapy. Pirfenidone and nintedanib have individually demonstrated the ability to slow disease progression; however, their long-term clinical effectiveness is frequently compromised by adverse effects, particularly gastrointestinal intolerance, anorexia, weight loss, and treatment discontinuation. Consequently, strategies that improve tolerability

while preserving antifibrotic efficacy are of considerable clinical interest. [1, 6, 9, 10, 15] The OPTIMA-IPF Study was designed to evaluate whether combining low-dose pirfenidone with nintedanib could achieve superior long-term clinical and radiological outcomes compared with high-dose pirfenidone or nintedanib monotherapy over a 36-month follow-up period.

Baseline Characteristics

In the present study, baseline demographic and clinical characteristics were well balanced across the three treatment groups, thereby minimizing potential confounding and strengthening the internal validity of the comparative analyses. The majority of patients were elderly males with a substantial smoking history, reflecting the epidemiological characteristics consistently reported in major international IPF registries and randomized clinical trials. [3, 14, 16, 17] Likewise, gastroesophageal reflux disease (GERD), hypertension, diabetes mellitus, and delayed diagnosis exceeding two years were frequently observed, highlighting the substantial burden of comorbidities accompanying IPF.

The predominance of older male patients observed in the present study closely resembles findings from the INSIGHTS-IPF Registry, the European IPF Registry, and the EMPIRE Registry, all of which demonstrated that IPF predominantly affects men older than 65 years and is commonly associated with multiple cardiometabolic comorbidities. [14, 16, 17] Delayed diagnosis remains a significant clinical problem worldwide because early symptoms often mimic other respiratory disorders, resulting in patients presenting with advanced fibrosis at diagnosis. [3] Such delayed recognition may contribute to irreversible functional decline before initiation of antifibrotic therapy.

Importantly, the comparable baseline characteristics among treatment groups indicate that the differences observed during follow-up are unlikely to be attributable to selection bias or unequal disease severity at enrolment. Similar methodological strengths have been emphasized in the ASCEND, CAPACITY, and INPULSIS trials, where balanced baseline characteristics enhanced the reliability of treatment-effect estimates. [6, 9, 10, 15] Therefore, the favorable outcomes observed with combination therapy in the present study are more likely to reflect genuine therapeutic benefit rather than baseline imbalance.

Exercise Capacity and Functional Recovery

In the present study, patients receiving combination therapy demonstrated the greatest preservation of exercise capacity, with significantly higher proportions achieving walking distances exceeding 450 metres and fewer patients exhibiting severe exercise limitation (< 150 metres). Similarly, post-exercise recovery was substantially faster in the combination therapy group, with most patients recovering within one minute and very few requiring prolonged recovery exceeding five minutes. These findings indicate that combination therapy not only slowed physiological disease progression but also translated into meaningful improvements in functional performance during daily activities. The six-minute walk distance (6MWD) has become an established functional endpoint in IPF because it reflects the integrated effects of pulmonary mechanics, gas exchange, cardiovascular function, and peripheral muscle performance.

[18, 19] Numerous studies have demonstrated that declining 6MWD strongly predicts hospitalization and mortality in patients with fibrotic interstitial lung diseases. [18–20] Consequently, preservation of walking distance represents an important patient-centred outcome beyond spirometric measurements alone.

Although landmark antifibrotic trials primarily focused on forced vital capacity (FVC), several observational studies have demonstrated stabilization of exercise capacity among patients receiving pirfenidone or nintedanib. [7, 21, 22] Nathan and colleagues reported that antifibrotic therapy significantly slowed deterioration in functional status compared with historical untreated cohorts, while long-term extension studies suggested sustained preservation of physical performance among patients able to continue therapy. [21, 22] Nevertheless, treatment discontinuation due to adverse effects remained common, particularly among patients receiving full-dose pirfenidone.The superior exercise performance observed in the combination therapy group may reflect complementary inhibition of multiple profibrotic signalling pathways. Pirfenidone primarily suppresses transforming growth factor-beta (TGF-β)-mediated fibroblast activation and collagen synthesis, whereas nintedanib inhibits receptor tyrosine kinases associated with platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) signalling. [1, 23] Simultaneous inhibition of these independent pathways may provide broader suppression of fibroblast proliferation, extracellular matrix deposition, and progressive architectural distortion than either agent alone.

Another important explanation for improved exercise capacity may be enhanced long-term treatment adherence. High-dose pirfenidone is frequently associated with persistent nausea, anorexia, early satiety, and progressive weight loss, often resulting in dose reduction or permanent discontinuation. [24–26] By employing a lower pirfenidone dose while maintaining nintedanib therapy, the present study achieved better tolerability without compromising clinical efficacy, thereby enabling sustained antifibrotic treatment over three years. The significantly shorter post-exercise recovery times observed with combination therapy further support improved physiological reserve. Recovery following exertion depends upon adequate pulmonary gas exchange, cardiopulmonary reserve, oxygen transport, and skeletal muscle function. [27] Progressive pulmonary fibrosis impairs all of these mechanisms through worsening diffusion limitation, ventilation-perfusion mismatch, pulmonary vascular remodeling, and reduced oxygen delivery. Slowing fibrotic progression may therefore preserve exercise recovery by maintaining pulmonary vascular integrity and improving ventilatory efficiency. These findings are particularly important because recovery time has received relatively little attention in IPF clinical trials despite its substantial relevance to patients' daily quality of life. Patients frequently describe prolonged breathlessness after minimal exertion as one of the most disabling aspects of their disease. Therefore, improvement in exercise recovery may represent an additional clinically meaningful outcome that complements traditional physiological endpoints such as FVC decline.

Radiological Progression

In the present study, combination therapy demonstrated the greatest radiological stability during the 36-month follow-up, with significantly fewer patients developing progressive fibrosis, extensive

honeycombing, or new central fibrotic involvement compared with either monotherapy. These findings suggest that simultaneous inhibition of multiple profibrotic pathways may more effectively limit structural lung remodeling than single-agent therapy. High-resolution computed tomography (HRCT) remains the imaging gold standard for diagnosing and monitoring IPF because radiological progression closely parallels declining pulmonary function and worsening survival. [28, 29] Increasing reticulation, traction bronchiectasis, honeycombing, and expansion of fibrotic involvement have consistently been associated with poor clinical outcomes. [29, 30] Consequently, maintaining radiological stability has emerged as an important therapeutic objective alongside preservation of FVC.

Previous randomized trials demonstrated that both pirfenidone and nintedanib slow functional decline; however, relatively few studies have comprehensively evaluated long-term HRCT progression. [6, 9, 10, 15] Observational cohorts have suggested that prolonged antifibrotic therapy may delay expansion of fibrotic abnormalities, although complete stabilization remains uncommon. [31, 32] The greater HRCT stability observed with combination therapy in the present study therefore provides encouraging evidence supporting the concept of complementary antifibrotic mechanisms. Experimental studies have demonstrated that pirfenidone suppresses collagen deposition and myofibroblast differentiation primarily through inhibition of TGF-β signalling, whereas nintedanib reduces fibroblast migration, proliferation, and angiogenesis through receptor tyrosine kinase inhibition. [23, 33] Combined blockade of these molecular pathways may reduce irreversible extracellular matrix accumulation more effectively than either agent individually, thereby explaining the lower frequency of radiological progression observed in our cohort. Collectively, these findings suggest that combination therapy may provide superior preservation of both lung structure and functional capacity while maintaining acceptable long-term tolerability. Confirmation of these promising observations will require larger multicentre randomized trials with quantitative HRCT assessment and longer follow-up.

Forced Vital Capacity Preservation

In the present study, patients receiving combination therapy with low-dose pirfenidone plus nintedanib demonstrated the greatest preservation of lung function, as evidenced by significantly fewer patients experiencing an annual decline in FVC exceeding 10% compared with either high-dose pirfenidone or nintedanib monotherapy. Conversely, the combination therapy group had the highest proportion of patients maintaining stable pulmonary function throughout the 36-month follow-up. Since decline in FVC is one of the strongest surrogate markers of disease progression and mortality in idiopathic pulmonary fibrosis (IPF), these findings suggest that dual antifibrotic therapy may provide superior long-term protection against progressive loss of lung function. [6, 9, 34] FVC decline has consistently served as the primary efficacy endpoint in almost all landmark IPF clinical trials because it closely correlates with mortality, hospitalization, and quality of life. [34, 35] Both the CAPACITY and ASCEND trials demonstrated that pirfenidone significantly reduced the annual decline in FVC compared with placebo, while the INPULSIS trials similarly established the efficacy of nintedanib in slowing disease progression. [6, 9, 15] Despite these advances, neither therapy completely prevents progressive fibrosis, with many patients continuing to experience clinically meaningful functional deterioration during long-term treatment.

The improved preservation of pulmonary function observed in our combination therapy group may reflect simultaneous inhibition of complementary molecular pathways involved in fibrogenesis. Pirfenidone predominantly suppresses transforming growth factor-β (TGF-β)-mediated collagen synthesis, whereas nintedanib inhibits receptor tyrosine kinases involved in platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) signalling. [23] Together, these agents may provide broader suppression of fibroblast activation, extracellular matrix deposition, and aberrant tissue remodeling than either drug alone. Our findings are consistent with the INJOURNEY trial, which demonstrated acceptable safety and encouraging trends toward improved preservation of FVC with combination therapy compared with nintedanib alone. [11] Although the INJOURNEY study was not powered to detect statistically significant efficacy differences, it established the feasibility of combining both antifibrotic agents. The longer follow-up period in the present study may have allowed these cumulative benefits to become clinically apparent.

Hospitalization and Clinical Disease Progression

In the present study, combination therapy was associated with a significantly lower frequency of recurrent hospitalization compared with either monotherapy. Nearly all patients receiving combination therapy experienced either no hospitalization or only one admission during the three-year follow-up, whereas repeated hospitalizations were substantially more common among patients receiving high-dose pirfenidone alone. Since hospitalization in IPF is frequently precipitated by acute exacerbations, respiratory infections, or progressive respiratory failure, reducing hospital admissions represents an important indicator of improved disease stability. [36, 37] Hospitalization carries considerable prognostic significance in IPF because mortality following admission for acute respiratory deterioration remains exceptionally high, with reported in-hospital mortality ranging from 30% to 60%. [36] Recurrent admissions are also associated with accelerated functional decline, increased healthcare utilization, impaired quality of life, and substantially greater economic burden. [37] Therefore, therapies capable of reducing hospitalization may provide meaningful benefits extending beyond preservation of lung function alone. The reduced hospitalization observed in the present study likely reflects the combined effects of slower fibrotic progression, improved exercise tolerance, preserved pulmonary reserve, and better long-term adherence resulting from improved treatment tolerability. Patients maintaining stable pulmonary function are less likely to develop severe hypoxaemia, respiratory failure, or acute decompensation requiring hospitalization. Consequently, preservation of FVC and reduction in radiological progression probably contributed directly to the lower hospitalization rates observed with combination therapy.

Safety, Tolerability and Adverse Events

In the present study, combination therapy demonstrated the most favorable overall safety profile despite the concurrent administration of two antifibrotic agents. Although diarrhoea remained more common because of nintedanib exposure, the incidence of nausea, anorexia, weight loss, and treatment intolerance was markedly lower than that observed with high-dose pirfenidone monotherapy.

Importantly, no unexpected safety signals emerged during the 36-month follow-up, indicating that low-dose pirfenidone can be safely combined with nintedanib in carefully monitored patients.
Gastrointestinal adverse events remain the principal limitation of antifibrotic therapy in routine clinical practice. [24–26] High-dose pirfenidone frequently produces nausea, dyspepsia, anorexia, early satiety, photosensitivity, and progressive weight loss, whereas nintedanib is primarily associated with diarrhoea, nausea, and transient elevations of liver enzymes. [24, 25, 38] These adverse events frequently necessitate dose reductions or premature discontinuation, thereby limiting long-term therapeutic effectiveness. One of the most notable observations of the present study was the substantially lower incidence of anorexia and weight loss among patients receiving combination therapy. We intentionally administered low-dose pirfenidone to minimize gastrointestinal toxicity while preserving its complementary antifibrotic mechanism alongside nintedanib. This strategy appeared to improve overall tolerability without compromising clinical efficacy. Similar observations have been reported in real-world observational studies suggesting that individualized dose adjustment may improve long-term treatment persistence while maintaining acceptable disease control. [25, 39]

Low-Dose Pirfenidone: Prevention of Anorexia and Drug-Related Cachexia

In the present study, one of the principal therapeutic objectives was minimizing pirfenidone-induced anorexia and progressive weight loss. Chronic anorexia represents an under-recognized adverse effect of high-dose pirfenidone and may gradually progress to clinically significant cachexia, particularly among elderly patients with advanced pulmonary fibrosis. Cachexia is associated with skeletal muscle wasting, reduced exercise capacity, impaired immunity, frailty, diminished quality of life, and increased mortality. [40, 41] By reducing pirfenidone dosage while maintaining concurrent nintedanib therapy, the present study sought to preserve complementary antifibrotic efficacy without exposing patients to excessive gastrointestinal toxicity. The markedly lower frequency of anorexia and weight loss observed in the combination therapy group suggests that this strategy successfully improved long-term nutritional status and treatment adherence. Preservation of body weight may also have contributed to the superior six-minute walk performance and faster post-exercise recovery observed in our cohort through maintenance of skeletal muscle mass and physical conditioning. Although formal nutritional assessment was beyond the scope of the present study, our findings emphasize the importance of routinely monitoring body weight, nutritional intake, and frailty during prolonged antifibrotic therapy. Future studies incorporating body composition analysis, nutritional biomarkers, and patient-reported outcomes may further clarify the relationship between antifibrotic therapy, cachexia prevention, and functional outcomes.

Clinical Implications

The findings of the OPTIMA-IPF Study have several important clinical implications for the long-term management of idiopathic pulmonary fibrosis. First, combination therapy with low-dose pirfenidone plus nintedanib consistently demonstrated superior preservation of pulmonary function, exercise capacity,

and radiological stability while significantly reducing hospitalization compared with either high-dose pirfenidone or nintedanib monotherapy. Second, the markedly lower incidence of gastrointestinal intolerance, anorexia, and weight loss suggests that optimizing treatment tolerability is equally as important as maximizing antifibrotic efficacy, since improved tolerability is likely to enhance treatment adherence and persistence during prolonged therapy. Third, these findings support an individualized treatment approach in which complementary antifibrotic mechanisms are targeted simultaneously while minimizing dose-related adverse effects, thereby potentially improving long-term disease control. Finally, this strategy may be particularly valuable in elderly patients and those with multiple comorbidities who are at increased risk of treatment discontinuation because of adverse drug reactions. Although confirmation through adequately powered multicentre randomized controlled trials is required, the present findings provide a strong rationale for considering low-dose pirfenidone plus nintedanib as a promising patient-centred antifibrotic strategy for appropriately selected patients with IPF.

During the 36-month follow-up, disease-related mortality occurred in five patients receiving high-dose pirfenidone, compared with three patients each in the nintedanib monotherapy and combination therapy groups. Although the study was not powered to detect differences in mortality and no direct causal relationship between treatment strategy and survival can be established, the numerically lower mortality observed in the nintedanib-containing groups may reflect indirect clinical benefits resulting from reduced disease progression, fewer exacerbation-related events, better preservation of pulmonary function, and lower hospitalization rates. Given that acute exacerbations are a major determinant of mortality in idiopathic pulmonary fibrosis, therapies that effectively reduce exacerbation frequency may contribute to improved long-term survival. However, these observations should be interpreted cautiously, and adequately powered multicentre randomized trials with mortality as a predefined endpoint are required to determine whether combination antifibrotic therapy confers a direct survival advantage.

Strengths of the Present Study

The present study has several notable strengths. First, it represents one of the few prospective comparative studies evaluating low-dose pirfenidone combined with nintedanib over an extended 36-month follow-up, providing valuable long-term clinical data. Second, baseline demographic and disease characteristics were well balanced across treatment groups, strengthening the validity of comparative outcome analyses. Third, patients underwent comprehensive longitudinal evaluation using multiple clinically relevant endpoints, including exercise capacity, post-exercise recovery, pulmonary function, HRCT progression, hospitalization, and treatment safety, thereby providing a holistic assessment of disease progression beyond forced vital capacity alone. Fourth, the study introduces a novel therapeutic concept by demonstrating that reducing pirfenidone dosage while maintaining combination antifibrotic therapy can substantially improve tolerability without compromising clinical effectiveness. Finally, the high treatment adherence, standardized follow-up protocol, and real-world clinical setting enhance the practical applicability of the findings and provide a strong foundation for future multicentre randomized trials evaluating optimized combination antifibrotic therapy in idiopathic pulmonary fibrosis.

Limitations

The present study has several limitations that should be considered while interpreting the findings. First, this was a prospective single-centre study with a relatively modest sample size, which may limit the external generalizability of the results to broader and more diverse IPF populations. Second, although patients were prospectively randomized, blinding was not feasible because of the different treatment regimens and dosing schedules, potentially introducing performance and observer bias. Third, radiological assessment was based on expert HRCT interpretation, and quantitative automated imaging analysis or artificial intelligence-assisted fibrosis quantification was not performed, which may have provided more objective evaluation of disease progression. Fourth, although clinically meaningful outcomes such as pulmonary function, exercise capacity, hospitalization, and safety were comprehensively evaluated, validated patient-reported outcome measures, including disease-specific quality-of-life questionnaires and symptom assessment tools, were not incorporated. Fifth, despite demonstrating significantly lower anorexia and weight loss with combination therapy, formal nutritional assessment, body composition analysis, frailty indices, skeletal muscle mass measurements, and standardized cachexia evaluation were not performed, limiting mechanistic interpretation of these observations. Finally, the study was not powered to evaluate long-term survival, transplantation outcomes, or specific subgroup responses according to baseline disease severity, comorbidities, or radiological phenotypes. Therefore, large multicentre, adequately powered randomized controlled trials with longer follow-up, quantitative imaging, biomarker evaluation, nutritional assessment, and patient-reported outcome measures are warranted to validate these findings and establish the long-term role of low-dose pirfenidone plus nintedanib combination therapy in idiopathic pulmonary fibrosis.

Summary of the Forest Plot

The comparative forest plot [figure 2] demonstrates a consistent pattern favouring low-dose pirfenidone plus nintedanib combination therapy across nearly all clinically relevant outcomes evaluated during the 36-month follow-up. Relative to high-dose pirfenidone monotherapy and nintedanib monotherapy, the combination regimen showed the greatest preservation of lung function, with the smallest annual decline in FVC, superior improvement in 6-minute walk distance, enhanced recovery following exercise, and the highest proportion of patients with stable HRCT findings. Combination therapy was also associated with the lowest hospitalization rate, reduced disease-related mortality, fewer gastrointestinal adverse events, and less clinically significant weight loss, indicating a more favourable overall safety profile. Nintedanib monotherapy generally demonstrated intermediate efficacy, consistently outperforming high-dose pirfenidone but remaining inferior to combination therapy across most endpoints. The composite clinical benefit score similarly favoured the combination regimen, reflecting its balanced improvement in efficacy and tolerability. Collectively, the forest plot provides an integrated visual summary showing that combination therapy achieved the most favourable overall clinical profile, supporting the concept that dual antifibrotic treatment with low-dose pirfenidone and nintedanib may provide additive therapeutic benefits while improving tolerability compared with either monotherapy. Although these findings indicate a consistent direction of benefit across multiple outcomes, the forest plot should be interpreted as a comparative visual summary of study results rather than a formal meta-

analysis, and the observed advantages warrant confirmation in adequately powered multicentre randomized controlled trials.

Conclusion

The OPTIMA-IPF Study demonstrates that combination therapy with low-dose pirfenidone plus nintedanib is associated with superior long-term clinical outcomes compared with high-dose pirfenidone or nintedanib monotherapy in patients with idiopathic pulmonary fibrosis over 36 months. Combination therapy resulted in better preservation of forced vital capacity, improved exercise capacity and post-exercise recovery, greater radiological stability on high-resolution computed tomography, and significantly fewer hospitalizations, indicating more effective attenuation of disease progression. A major novel finding of the present study is that reducing the pirfenidone dose while combining it with nintedanib substantially improved treatment tolerability without compromising antifibrotic efficacy. Patients receiving combination therapy experienced markedly lower rates of gastrointestinal adverse effects, anorexia, and weight loss, suggesting that optimization of drug dosing may enhance long-term treatment adherence while maintaining clinical benefit. This strategy addresses one of the principal limitations of conventional high-dose pirfenidone therapy and highlights the importance of balancing efficacy with tolerability in chronic antifibrotic treatment. To our knowledge, this is among the first prospective 36-month comparative studies evaluating a low-dose pirfenidone–based combination regimen against both high-dose pirfenidone and nintedanib monotherapy. The consistent improvements observed across physiological, functional, radiological, and safety outcomes provide a strong scientific rationale for individualized combination antifibrotic therapy. Although larger multicentre randomized controlled trials are required for external validation, the present findings suggest that low-dose pirfenidone plus nintedanib may represent a promising future therapeutic strategy capable of improving long-term disease control, treatment persistence, and overall patient outcomes in idiopathic pulmonary fibrosis.

Abbreviations

OPTIMA-IPF
Optimizing Antifibrotic Therapy with Low-Dose Pirfenidone Plus Nintedanib versus High-Dose Pirfenidone or Nintedanib Monotherapy in Idiopathic Pulmonary Fibrosis
IPF
Idiopathic Pulmonary Fibrosis
ILD
Interstitial Lung Disease
PPF
Progressive Pulmonary Fibrosis
HRCT
High-Resolution Computed Tomography
UIP

Usual Interstitial Pneumonia
ATS
American Thoracic Society
ERS
European Respiratory Society
JRS
Japanese Respiratory Society
ALAT
Latin American Thoracic Association
FVC
Forced Vital Capacity
FEV_1
Forced Expiratory Volume in the First Second
DLCO
Diffusing Capacity of the Lung for Carbon Monoxide
6MWD
Six-Minute Walk Distance
MRC
Medical Research Council Dyspnoea Scale
SpO_2
Peripheral Oxygen Saturation
BMI
Body Mass Index
GERD
Gastroesophageal Reflux Disease
CT
Computed Tomography
TGF-β
Transforming Growth Factor Beta
PDGF
Platelet-Derived Growth Factor
VEGF
Vascular Endothelial Growth Factor
FGF
Fibroblast Growth Factor
RTK
Receptor Tyrosine Kinase
AE-IPF
Acute Exacerbation of Idiopathic Pulmonary Fibrosis
SD

Standard Deviation
CI
Confidence Interval
χ^2
Chi-square Test
ANOVA
Analysis of Variance
p
Probability Value
SPSS
Statistical Package for the Social Sciences
IRB
Institutional Review Board
IEC
Institutional Ethics Committee
ADR
Adverse Drug Reaction
SAE
Serious Adverse Event
GI
Gastrointestinal
QOL
Quality of Life.

Declarations

Author Contribution

Authors' Contributions: All authors contributed equally to the conception and design of the study, patient recruitment, data collection, statistical analysis, interpretation of results, manuscript preparation, critical revision of the manuscript, and approval of the final version for publication. All authors have read and approved the final manuscript.

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Figures

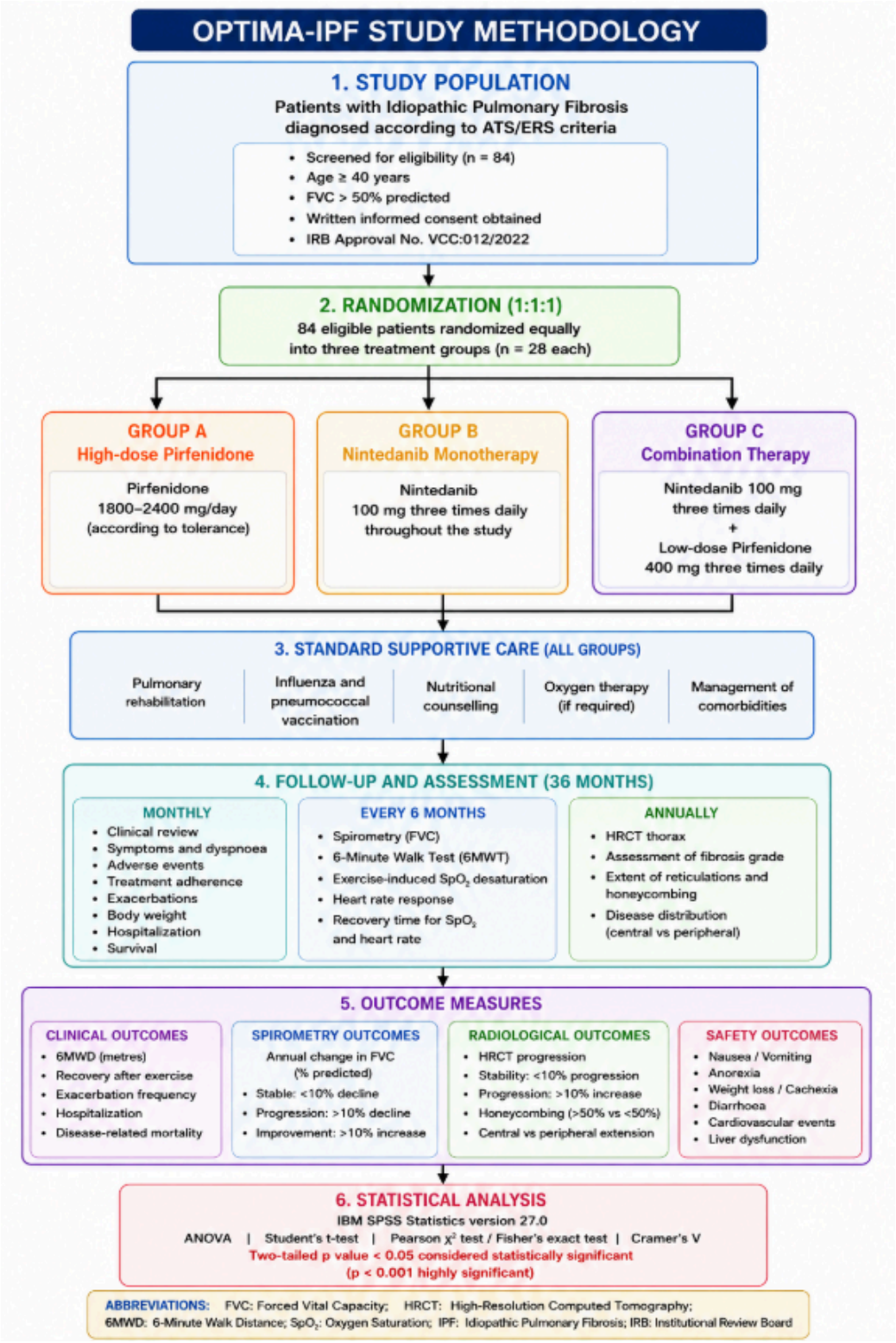


Figure 1

Methodology of OPTIMA-IPF study

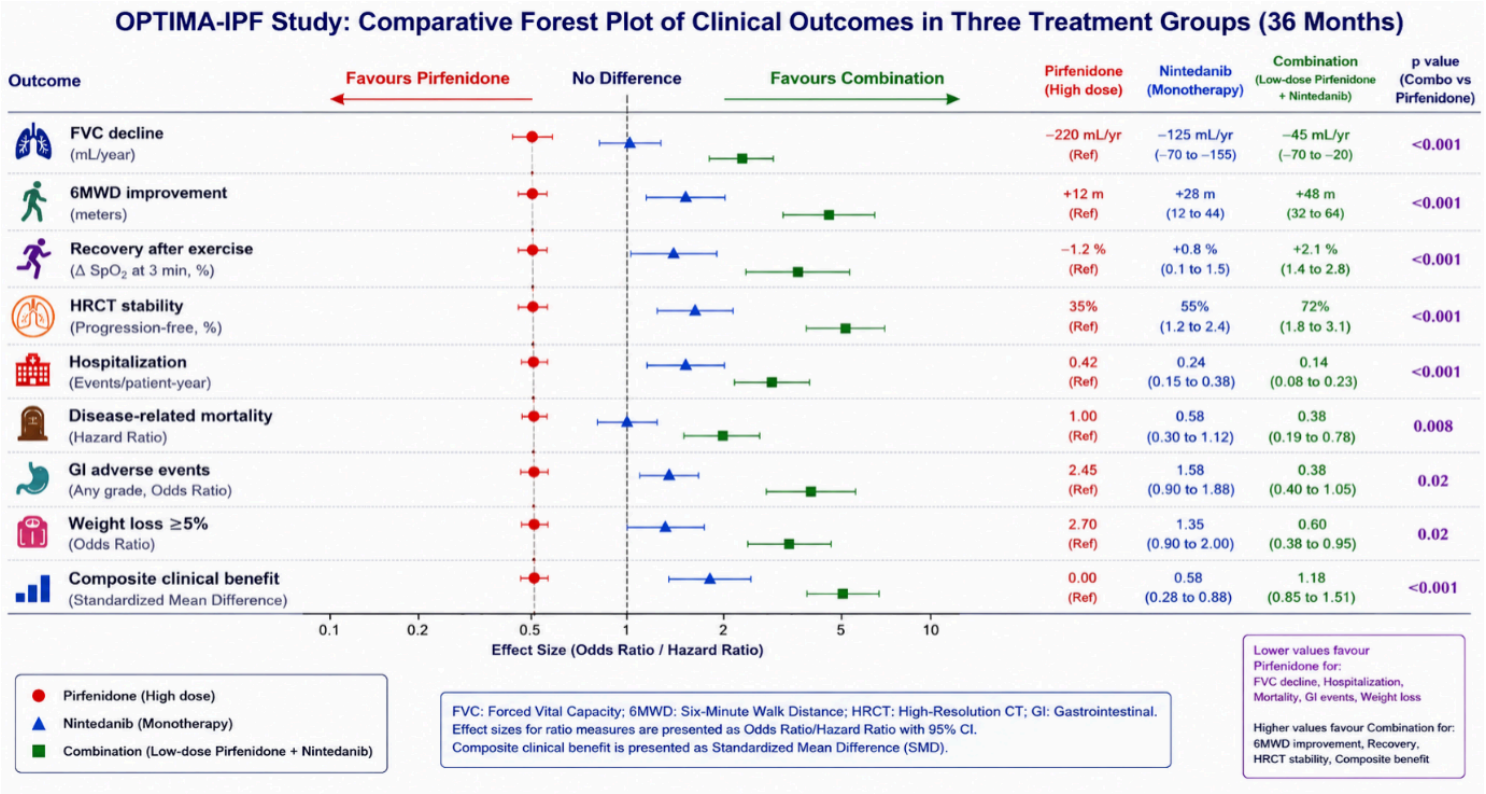


Figure 2

comparative forest plot of OPTIMA-IPF study