Supplementary tables

Table S1

Inclusion and exclusion criteria.

Inclusion criteria
Written informed consent
Male or female patients aged ≥ 18 years
Patients with physician-diagnosed ILD who fulfil at least one of the following criteria for PF-ILD within 24 months of screening despite treatment with unapproved medications used in clinical practice to treat ILD: • Clinically significant decline in FVC % pred based on a relative decline of ≥ 10% • Marginal decline in FVC % pred based on a relative decline of ≥ 5 – < 10% combined with worsening respiratory symptoms • Marginal decline in FVC % pred based on a relative decline of ≥ 5 – < 10% combined with increasing extent of fibrotic changes on chest imaging • Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging Changes attributable to comorbidities (eg infection, heart failure) must be excluded Unapproved medications used to treat ILD in clinical practice include, but are not limited to, corticosteroids, azathioprine, mycophenolate mofetil, n-acetylcysteine, rituximab, cyclophosphamide, cyclosporine and tacrolimus
Fibrosing lung disease on HRCT (performed within 12 months of screening and confirmed by central readers), defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of > 10%
For patients with underlying CTD: Stable CTD, defined as no initiation of new CTD therapy or withdrawal of CTD therapy within 6 weeks before screening
DLCO corrected for haemoglobin ≥ 30% and < 80% of predicted normal at randomisation
FVC ≥ 45% predicted at randomisation
Exclusion criteria
AST, ALT > 1.5 × ULN at screening*
Bilirubin > 1.5 × ULN at screening*
Creatinine clearance < 30 mL/min*
Chronic liver disease (Child Pugh A, B or C hepatic impairment)
Previous treatment with nintedanib or pirfenidone
Other investigational therapy received within 1 month or 6 half-lives (whichever is

greater) before screening
Use of any of the following medications to treat ILD: azathioprine; cyclosporine; mycophenolate mofetil; tacrolimus; oral corticosteroids (> 20 mg/day) or the combination of oral corticosteroids + azathioprine + n-acetylcysteine (within 4 weeks of randomisation); cyclophosphamide (within 8 weeks of randomisation); or rituximab (within 6 months of randomisation)
Diagnosis of IPF based on ATS/ERS/JRS/ALAT 2011 Guidelines
Significant pulmonary arterial hypertension defined by any of the following: • Previous clinical or echocardiographic evidence of significant right heart failure • History of right heart catheterisation showing a cardiac index ≤ 2 l/min/m² • Requirement for parenteral therapy with epoprostenol/treprostinil
Primary obstructive airway physiology (pre-bronchodilator $FEV_1/FVC < 0.7$ at screening)
Other clinically significant pulmonary abnormalities (in the opinion of the investigator)
Major extra-pulmonary physiological restriction (eg chest wall abnormality, large pleural effusion)
Any of the following cardiovascular diseases within 6 months of screening: • Severe hypertension, uncontrolled by treatment (≥ 160/100 mmHg) • Myocardial infarction • Unstable cardiac angina
Risk of bleeding as a result of any of the following: • Known genetic predisposition to bleeding • Patients requiring fibrinolysis, full-dose therapeutic anticoagulation (eg vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin) or high-dose antiplatelet therapy** • History of haemorrhagic central nervous system event within 12 months of screening • Haemoptysis or haematuria, active gastrointestinal bleeding or ulcers, major injury or surgery (in the opinion of the investigator) within 3 months of screening • INR > 2, prolongation of prothrombin time and aPTT > 1.5 × ULN at screening
History of a thrombotic event (including stroke and transient ischaemic attack) within 12 months of screening
Known hypersensitivity to the trial medication or its components (ie soya lecithin)
Peanut allergy
Other disease that may interfere with the testing procedures or (in the opinion of the investigator) with trial participation or may put the patient at risk when participating

in the trial
Life expectancy for disease other than ILD < 2.5 years (investigator's assessment)
Planned major surgical procedures
Women who are pregnant, nursing or who plan to become pregnant during the trial
Women of childbearing potential not willing or able to use highly effective methods of birth control that result in a low failure rate of less than 1% per year (when used consistently and correctly) and one barrier method for 28 days before and 3 months after nintedanib administration
Active alcohol or drug abuse (in the opinion of the investigator)
Patients not able to understand or follow trial procedures (including completion of self-administered questionnaires) without help

Abbreviations: % pred, per cent predicted; ALAT, Latin American Thoracic Association; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; ATS, American Thoracic Society; CTD, connective tissue disease; DLCO, diffusing capacity of the lungs for carbon monoxide; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; INR, international normalised ratio; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; PF-ILD, progressive fibrosing interstitial lung disease; ULN, upper limit of normal.

[*] = Results for these parameters at Visit 2 (randomisation) will only become available after randomisation; if they no longer satisfy the entry criteria, entry of the patient is at the discretion of the investigator.

[**] = Prophylactic low-dose heparin or heparin flush for maintenance of an indwelling intravenous device and prophylactic use of antiplatelet therapy are not prohibited.

Table S2

Power properties for varying treatment differences in the two co-primary populations.

	Patients with HRCT with UIP-like fibrotic pattern only (co-primary)	**Patients with other HRCT fibrotic patterns**	**Overall patient population** (co-primary)	
Scenario 1				
Assumed treatment difference in absolute change in FVC in mL/year (SD)	100 (300)	75 (400)	92 (337)	
Individual test power	90.2%		90.3%	
Overall power*				92.6%
Scenario 2				
Assumed treatment difference in absolute change in FVC in mL/year (SD)	75 (300)	60 (400)	70 (337)	
Individual test power	67.2%		68.2%	
Overall power*				72.4%

Scenario 3				
Assumed treatment difference in absolute change in FVC in mL/year (SD)	75 (300)	75 (400)	75 (337)	
Individual test power	68.2%		73.4%	
Overall power*				75.8%

Abbreviations: FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; PF-ILD, progressive fibrosing ILD; SD, standard deviation; UIP, usual interstitial pneumonia.

* = The probability of concluding statistical significance for either of the co-primary populations.

For scenario planning, annual rates of decline in FVC of 150-200 mL/year and 120-150 mL/year have been assumed for PF-ILD patients with UIP-like HRCT pattern and for patients with other HRCT fibrotic patterns, respectively.

Based on the IPF data, in patients treated with nintedanib, an approximate 50% reduction in the annual rate of decline in FVC is expected. The treatment effect to detect is therefore in the range of 75-100 mL/year for the PF-ILD patients with UIP-like HRCT pattern and of 60-75 mL/year in the PF-ILD patients with other HRCT fibrotic patterns.

For patients with other HRCT fibrotic patterns, the variability is assumed to be larger than in IPF with a SD of 400 mL/year. For patients with UIP-like HRCT pattern, a more homogeneous group of patients, the variability is assumed to be the same as observed in IPF with a SD of 300 mL/year.

Therefore, the proposed sample size of 300 patients randomised per treatment group, ie 600 patients in total, including 400 patients with UIP-like HRCT pattern, will provide adequate power to demonstrate a clinically important treatment benefit on the primary endpoint even in scenarios where the annual rate of decline in both co-primary patient populations is lower than observed for IPF patients in the Phase III IPF trials.

Table S3

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