Progressive Pulmonary Fibrosis: Current Status in Terminology and Future Directions

Running title: PPF terminology

Authors: Yasuhiro Kondoh,[1,2] Yoshikazu Inoue[3,4]

Affiliations:

[1]Department of Respiratory Medicine and Allergology, Aichi Medical School, Aichi, Japan

[2]Department of Respiratory Medicine and Allergy, Tosei General Hospital, Aichi, Japan

[3]Osaka Anti-tuberculosis Association, Osaka Fukujuji Hospital, Osaka, Japan

[4]Clinical Research Center, NHO Kinki Chuo Chest Medical Center, Osaka, Japan

Corresponding author:

Yasuhiro Kondoh, M.D., Ph.D.

Department of Respiratory Medicine and Allergology,

Aichi Medical School, 1-1 Yazakokarimata,

Nagakute, Aichi 480-1195, Japan.

Email: yshr.kondoh@gmail.com

Supplementary Appendix

Table S1. Eligibility Criteria from Pivotal Trials Evaluating Antifibrotic Therapy in Progressive Pulmonary Fibrosis

Drug	Study Name (Study ID) / Study Dates	Inclusion criteria	Main exclusion criteria
Treprostinil	**RIN-PF-305 (NCT05943535)** Study start: 30 Oct 2023 Primary Completion: Nov 2027 Study Completion: Nov 2027	• Clinically significant decline in % predicted FVC based on ≥10% relative decline; • Marginal decline in % predicted FVC based on ≥5%–<10% relative decline + worsening of respiratory symptoms; • Marginal decline in % predicted FVC based on ≥5%–<10% relative decline + increasing extent of fibrotic changes on chest imaging; • Worsening respiratory symptoms + increasing extent of fibrotic changes on chest imaging; • Patients must also be on 1 of the following: – Nintedanib or pirfenidone for ≥90 days and planning to continue treatment through the study – Not on treatment with nintedanib or pirfenidone for ≥90 days and not planning to initiate either treatment during the study. • Concomitant use of nintedanib and pirfenidone not permitted.	• Primary obstructive airway physiology (FEV1/FVC <0.70 at screening) or greater extent of emphysema than fibrosis on HRCT. • FVC <45% predicted.
Admilparant/BMS-986278	NCT06025578 Study start: 25 Oct 2023 Primary Completion: 27 Dec 2027 Study Completion: 27 Dec 2027	• ILD diagnosis with features consistent with progressive ILD ≤24 months AND ≥10% fibrosis on screening HRCT. • If on pirfenidone or nintedanib, must have been on a stable dose for ≥90 days. • If not currently on pirfenidone or nintedanib, must not have received either of these medications ≤28 days.	• IPF with usual interstitial pneumonia verification at screening. • Use of systemic corticosteroids equivalent to prednisone >15 mg/day not permitted ≤4 weeks prior to screening and during the

			study.
Nerandomilast/BI 1015550	**NCT05321082** Study start: 5 Oct 2022 Primary Completion: 9 Dec 2024 Study Completion: 19 Mar 2025	• FVC ≥45% predicted. • DL_{CO} ≥25% predicted corrected for Hb. • Presence of fibrotic lung disease with disease extent >10% on HRCT performed ≤12 months of visit 1 as confirmed by central review. • Patients with pulmonary fibrosis other than IPF who manifest progression according to ≥1 of the following predefined criteria ≤24 months of visit 1: – Relative decline in FVC% predicted of ≥10%. – Decline in FVC% of ≥5%–<10% with worsening of respiratory symptoms. – Decline in FVC% predicted of ≥5%–<10% with increasing extent of fibrotic changes on chest imaging. – Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging. • Patients may be either: – On a stable therapy[a] with nintedanib for ≥12 weeks and are planning to stay on this background treatment after randomization. (*defined as a tolerated regimen with no dose changes for ≥12 weeks); – Not on nintedanib treatment for ≥8 weeks (e.g. either antifibrotic-treatment naïve or previously discontinued) and do not plan to start/re-start antifibrotic treatment. • Patients on stable treatment with certain immunosuppressives other than corticosteroids (eg, methotrexate, azathioprine) for ≥12 weeks	• FEV1/FVC <0.7 at Visit 1. • Other clinically significant pulmonary abnormalities. • Acute ILD exacerbation ≤3 months prior to Visit 1 and/or during the screening period (investigator-determined). • ILD due to SARS-CoV-2 infection/COVID-19 ≤12 months of screening

		for an underlying systemic disease were permitted.	
Inhaled AP01 (pirfenidone solution for inhalation)	NCT06329401 Study start: 3 Apr 2024 Primary Completion: Apr 2026 Study Completion: Apr 2026	• ≥1 of the following criteria despite treatment: – Relative decline in FVC ≥10% predicted ≤previous 24 months – Relative decline in FVC ≥5–<10% predicted ≤previous 24 months with at least 1 of the 2 following criteria: ▪ Worsening respiratory symptoms (Changes attributable to comorbidities e.g., infection, heart failure must be excluded); OR ▪ Radiological evidence of progression on HRCT[a] • Meeting all of the following criteria during the screening period: – a. FVC ≥45% of predicted normal; – b. FEV1/FVC ≥0.7 or ≥age-adjusted LLN; – c. DL_{CO} ≥30% of predicted, corrected for Hb; • Patients with ILD other than IPF who have radiological evidence of PF[a] • Physiological evidence of PD ▪ Worsening of respiratory symptoms AND radiological (HRCT) evidence of PD[a] • Patients can perform acceptable spirometry (i.e., meet ATS/ERS acceptability criteria). • For patients already on nintedanib (≤30% of subjects), must have been on nintedanib for ≥6 months with or without dose adjustments and/or drug interruptions. • For patients who have discontinued nintedanib prior to screening, must have been off of nintedanib for ≥12 weeks.	• Current treatment with oral pirfenidone or treatment with oral pirfenidone ≤3 months prior to screening. • Diagnosis of IPF based on the ATS diagnostic algorithm for IPF. • Greater extent of emphysema than of fibrotic ILD on HRCT. • Significant clinical worsening of PPF between screening. • Patients who cannot meet protocol-specified baseline stability criteria, defined as the FVC assessments at Visit 3 being within ±12% of the mean of the FVC assessments obtained at the 2 preceding visits. At Visit 3, if the pre-dose FVC is outside of ±12% range, the patient will not be randomized and will be considered a screen failure.

Yifenidone/HEC585	NCT05139719 Study start: 15 Feb 2023 Primary Completion: Dec 2024 Study Completion: Dec 2026	• ≥2 of the following criteria ≤12 months: – absolute FVC (% of predicted) decline ≥5%; – absolute DLco (Hb corrected) (% of predicted) decline ≥10%. • FEV1/FVC ≥0.7 before bronchodilators. • %FVC ≥45% predicted. • DL_{CO} corrected for Hb ≥30% and ≤80% predicted. • Known or unknown etiology (except IPF) and clear PF on chest CT • Radiological evidence of PD[a,b]	• Diagnosis of IPF • Significant PAH. • Major extrapulmonary physiological or pathological restriction (e.g. chest wall abnormality, large pleural effusion). • Expected survival <6 months. • Use of any of the following medications: – Strong inducers or inhibitors of CYP3A4 ≤4 weeks before randomization. – Immunosuppressants – Pirfenidone or nintedanib ≤1 months before screening.

ATS, American Thoracic Society; COVID-19, coronavirus disease 2019; CYP3A4, Cytochrome P450 3A4; DL_{CO}, diffusing capacity of lung for carbon monoxide; ERS, European Respiratory Society; FEV, forced expiratory volume; FEV1, Forced expiratory volume at 1 second; FVC, forced vital capacity; Hb, hemoglobin; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PAH, Pulmonary Arterial Hypertension; PD, progressive disease; PF, progressive fibrosis; PPF, progressive pulmonary fibrosis; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2.

[a]Defined as increased extent or severity of traction bronchiectasis and bronchiolectasis, new ground-glass opacity with traction bronchiectasis, new fine reticulation, increased extent or increased coarseness of reticular abnormality, new or increased honeycombing, or increased lobar volume loss

[b]Defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%.