Nerandomilast in patients with idiopathic pulmonary fibrosis.

Luca Richeldi,[1] Arata Azuma,[2,3] Vincent Cottin,[4] Michael Kreuter,[5] Toby M Maher,[6,7] Fernando J Martinez,[8] Justin M Oldham,[9] Claudia Valenzuela,[10] Emmanuelle Clerisme-Beaty,[11] Maud Gordat,[12] Daniel Wachtlin,[13] Yi Liu,[14] Christina Schlecker,[15] Susanne Stowasser,[11] Donald F Zoz,[16] Marlies S Wijsenbeek,[17] for the FIBRONEER-IPF trial investigators.

1. Unità Operativa Complessa di Pneumologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; 2. Clinical Research Center, Mihara General Hospital, Saitama, Japan; 3. Nippon Medical School, Tokyo, Japan; 4. National Reference Center for Rare Pulmonary Diseases, Louis Pradel Hospital, Hospices Civils de Lyon, Claude Bernard University Lyon 1, UMR 754, ERN-LUNG, Lyon, France; 5. Center for Pulmonary Medicine, Department of Pneumology, Mainz University Medical Center and Pulmonary, Critical Care & Sleep Medicine, Marienhaus Clinic Mainz, Mainz, Germany; 6. Department of Pulmonary, Critical Care and Sleep Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA; 7. Section of Inflammation, Repair and Development, National Heart and Lung Institute, Imperial College London, London, UK; 8. University of Massachusetts (UMass) Chan Medical School/UMass Memorial Health System, Worcester, Massachusetts, USA; 9. Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Michigan, USA; 10. Pulmonology Department, Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, Madrid, Spain; 11. Therapy Area Inflammation Medicine, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; 12. Clinical Development & Operation Department, Boehringer Ingelheim, Reims, France; 13. Department of Biostatistics and Data Sciences, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; 14. Department of Biostatistics and Data Sciences, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut, USA; 15. Global Patient Safety and Pharmacovigilance, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; 16. Global Clinical Development and Medical Affairs, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut, USA; 17. Center of Expertise for Interstitial Lung Diseases, Department of Respiratory Medicine, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands.

Objective

The Phase III FIBRONEER-IPF trial investigated the efficacy and safety of nerandomilast 9 mg bid and 18 mg bid, as monotherapy or with background nintedanib or pirfenidone, in patients with IPF.

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Introduction

- IPF is a fibrosing interstitial lung disease characterized by progressive decline in lung function and high mortality.[1]
- Nintedanib and pirfenidone slow decline in lung function in patients with IPF[2,3] and have become the standard of care. However, these drugs do not halt progression, and have gastro-intestinal side-effects that often result in discontinuation.[2,3]
- Nerandomilast is an orally administered preferential inhibitor of phosphodiesterase 4B that has antifibrotic and immunomodulatory properties.[4,5]
- In a Phase II trial in 147 patients with IPF, nerandomilast 18 mg bid stabilized lung function over 12 weeks, with acceptable safety and tolerability.[6]

Methods

- FIBRONEER-IPF was a randomized, double-blind, placebo-controlled trial. Eligible patients were aged ≥40 years, had IPF with a UIP or probable UIP pattern on HRCT, FVC ≥45% predicted and DLco ≥25% predicted.
- Patients had taken nintedanib or pirfenidone at a stable dose for ≥12 weeks or had not taken nintedanib or pirfenidone for ≥8 weeks.
- Patients were randomized 1:1:1 to receive nerandomilast 9 mg bid, nerandomilast 18 mg bid, or placebo, stratified by background therapy (nintedanib/pirfenidone vs neither).
- The primary endpoint was the absolute change from baseline in FVC (mL) at week 52. Patients continued to take randomized blinded treatment until the end of the trial. The first database lock took place after the last patient completed the week 52 visit.
- The key secondary endpoint was time to first acute exacerbation, hospitalization for respiratory cause, or death, over the duration of the trial. Acute exacerbations and hospitalizations for respiratory cause were not adjudicated.

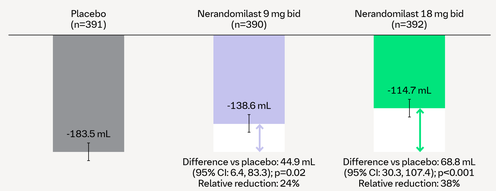
Results

Baseline characteristics (n=1177)

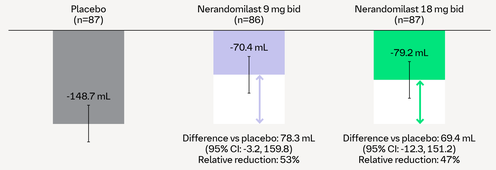
Male: **83.0%**	Mean age: **70.2 years**	Ever smokers: **71.0%**	Mean time since IPF diagnosis: **3.5 years**
Mean FVC % predicted: **78.2**	Mean DLco % predicted: **50.9**	Using supplemental oxygen: **21.1%**	Nintedanib: **45.5%*** Pirfenidone: **32.3%†** None: **22.3%**

*Among patients taking nintedanib, in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively, the mean time on nintedanib at baseline was 28.9, 27.7 and 27.4 months and the dose of nintedanib was 300 mg/day in 73.4%, 67.4% and 67.4% of patients.
†Among patients taking pirfenidone, in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively, the mean time on pirfenidone at baseline was 35.0, 32.6 and 30.9 months and the dose of pirfenidone was 2400 mg/day in 59.4%, 61.7% and 63.8% of patients.

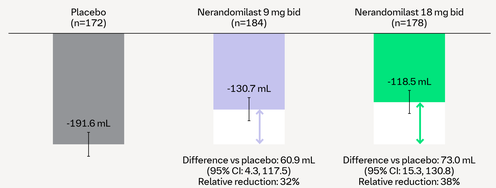
Change in FVC at week 52 (primary endpoint)



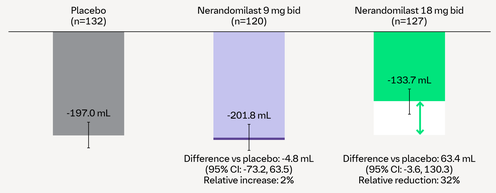
Change in FVC at week 52 in patients not taking background nintedanib or pirfenidone



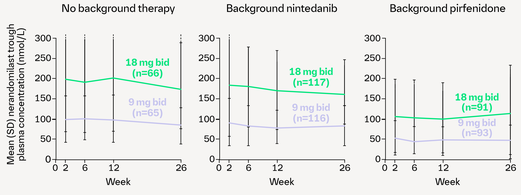
Change in FVC at week 52 in patients taking background nintedanib



Change in FVC at week 52 in patients taking background pirfenidone

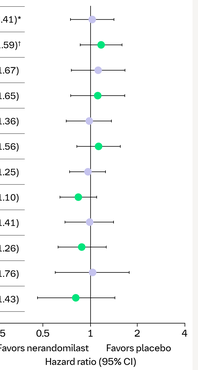


Plasma concentration-time profiles of nerandomilast by background therapy



Key secondary endpoint and other secondary time-to-event endpoints up to first database lock

		n (%) with event		Hazard ratio (95% CI)
		Placebo	Nerandomilast	
Key secondary endpoint	Nerandomilast 9 mg bid	80 (20.4)	79 (20.2)	1.03 (0.75, 1.41)*
	Nerandomilast 18 mg bid	80 (20.4)	85 (21.7)	1.17 (0.86, 1.59)†
First acute exacerbation or death	Nerandomilast 9 mg bid	49 (12.5)	51 (13.0)	1.12 (0.76, 1.67)
	Nerandomilast 18 mg bid	49 (12.5)	50 (12.8)	1.11 (0.75, 1.65)
First hospitalization for respiratory cause or death	Nerandomilast 9 mg bid	73 (18.6)	68 (17.3)	0.98 (0.70, 1.36)
	Nerandomilast 18 mg bid	73 (18.6)	75 (19.1)	1.13 (0.82, 1.56)
Absolute decline in FVC predicted >10% or death	Nerandomilast 9 mg bid	111 (28.2)	107 (27.3)	0.96 (0.74, 1.25)
	Nerandomilast 18 mg bid	111 (28.2)	94 (24.0)	0.84 (0.64, 1.10)
Absolute decline in DLco predicted >15% or death	Nerandomilast 9 mg bid	66 (16.8)	59 (15.1)	0.98 (0.69, 1.41)
	Nerandomilast 18 mg bid	66 (16.8)	59 (15.1)	0.88 (0.62, 1.26)
Death	Nerandomilast 9 mg bid	28 (7.1)	26 (6.6)	1.03 (0.60, 1.76)
	Nerandomilast 18 mg bid	28 (7.1)	21 (5.4)	0.81 (0.46, 1.43)



Mean exposure to trial medication up to first database lock was 13.3 months.
*p=0.86.
†p=0.31.

Adverse event (AE) summary over 52 weeks by background therapy

	No background therapy			Background nintedanib			Background pirfenidone		
	Placebo (N = 87)	Nerandomilast 9 mg bid (N = 88)	Nerandomilast 18 mg bid (N = 87)	Placebo (N = 173)	Nerandomilast 9 mg bid (N = 184)	Nerandomilast 18 mg bid (N = 178)	Placebo (N = 133)	Nerandomilast 9 mg bid (N = 120)	Nerandomilast 18 mg bid (N = 127)
AE(s)	83 (95.4)	77 (87.5)	79 (90.8)	163 (94.2)	175 (95.1)	174 (97.8)	125 (94.0)	112 (93.3)	119 (93.7)
Diarrhea AE(s)	7 (8.0)	15 (17.0)	23 (26.4)	46 (26.6)	91 (49.5)	110 (61.8)	10 (7.5)	16 (13.3)	29 (22.8)
AE(s) leading to treatment discontinuation	7 (8.0)	7 (8.0)	6 (6.9)	22 (12.7)	31 (16.8)	38 (21.3)	13 (9.8)	8 (6.7)	11 (8.7)
Diarrhea AE(s) leading to treatment discontinuation	0 (0)	0 (0)	1 (1.1)	2 (1.2)	4 (2.2)	23 (12.9)	0 (0)	3 (2.5)	0 (0)
Serious AE(s)*	28 (32.2)	22 (25.0)	20 (23.0)	50 (28.9)	62 (33.7)	56 (31.5)	53 (39.8)	37 (30.8)	41 (32.3)
Fatal AE(s)	7 (8.0)	3 (3.4)	0 (0)	5 (2.9)	9 (4.9)	4 (2.2)	6 (4.5)	4 (3.3)	2 (1.6)

Data are n (%) of patients with ≥1 such adverse event reported over 52-week treatment period or until 7 days after the last dose in patients who discontinued treatment before week 52.
*Event that resulted in death, in hospitalization or prolongation of hospitalization, or in persistent or clinically significant disability or incapacity; or was life-threatening, a congenital anomaly or birth defect, or deemed to be serious for any other reason.

Conclusions

- Both the 9 mg bid and 18 mg bid doses of nerandomilast were associated with a significant reduction in decline in FVC over 52 weeks.
- A drug-drug interaction meant that only the 18 mg bid dose of nerandomilast was effective in patients taking background pirfenidone.
- Nerandomilast had an acceptable safety and tolerability profile both when used as monotherapy and as add-on to background therapy.

Abbreviations
bid, twice daily. CI, confidence interval. DLco, diffusion capacity of the lungs for carbon monoxide. FVC, forced vital capacity. IPF, idiopathic pulmonary fibrosis. SD, standard deviation. SE, standard error. UIP, usual interstitial pneumonia.

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