Meta-Analysis of Effect of Nintedanib on Reducing FVC Decline Across Interstitial Lung Diseases

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ABSTRACT

Introduction: The effect of nintedanib on slowing the rate of decline in forced vital capacity (FVC) has been investigated in randomized placebo-controlled trials in subjects with idiopathic pulmonary fibrosis (IPF), other progressive fibrosing interstitial lung diseases (ILDs), and ILD associated with systemic sclerosis (SSc-ILD). We assessed the consistency of the effect of nintedanib on the rate of decline in FVC over 52 weeks across four placebo-controlled phase III trials.

Methods: We used data on FVC decline from the INPULSIS-1 and INPULSIS-2 trials in subjects with IPF, the INBUILD trial in subjects with progressing fibrosing ILDs other than IPF, and the SENSCIS trial in subjects with SSc-ILD. In each trial, the primary endpoint was the annual rate of decline in FVC (mL/year) assessed over 52 weeks. We performed fixed effect and random effects meta-analyses based on the relative treatment effect of nintedanib versus placebo on the rate of decline in FVC (mL/year) over 52 weeks. Heterogeneity of the relative treatment effect of nintedanib across populations was assessed using the I^2 statistic, τ^2 and corresponding p value from a Q test for heterogeneity.

Results: The combined analysis comprised 1257 subjects treated with nintedanib and 1042 subjects who received placebo. Nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks by 51.0% (95% CI 39.1, 63.0) compared with placebo. The relative effect

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(95% CI) was the same using the fixed effect and random effects models. There was no evidence of heterogeneity in the relative treatment effect of nintedanib across the populations studied ($I^2 = 0\%$, $\tau^2 = 0$, $p = 0.93$).

Conclusions: A meta-analysis of data from four placebo-controlled trials demonstrated that nintedanib approximately halved the rate of decline in FVC over 52 weeks across subjects with different forms of pulmonary fibrosis, with no evidence of heterogeneity in its relative treatment effect across patient populations.

Graphical abstract:

Meta-analysis of effect of nintedanib on reducing FVC decline across interstitial lung diseases (ILDs)

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Introduction

The effect of nintedanib on the rate of decline in FVC has been investigated in placebo-controlled trials in subjects with IPF, other progressive fibrosing ILDs and systemic sclerosis-associated ILD (SSc-ILD)
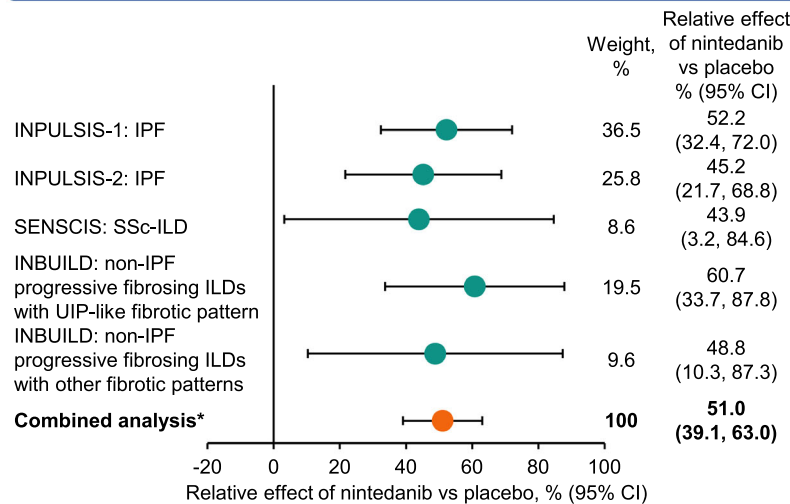
Aim

To assess whether the effect of nintedanib on slowing the rate of decline in FVC was consistent across a spectrum of fibrosing ILDs

Methods

Fixed effect and random effects meta-analyses were performed based on the relative treatment effect of nintedanib versus placebo on the rate of decline in FVC (mL/year) over 52 weeks in the INPULSIS, SENSCIS and INBUILD trials

Relative effect of nintedanib vs placebo on the rate of FVC decline (mL/year) over 52 weeks in the INPULSIS, SENSCIS and INBUILD trials

	Weight, %	Relative effect of nintedanib vs placebo % (95% CI)
INPULSIS-1: IPF	36.5	52.2 (32.4, 72.0)
INPULSIS-2: IPF	25.8	45.2 (21.7, 68.8)
SENSCIS: SSc-ILD	8.6	43.9 (3.2, 84.6)
INBUILD: non-IPF progressive fibrosing ILDs with UIP-like fibrotic pattern	19.5	60.7 (33.7, 87.8)
INBUILD: non-IPF progressive fibrosing ILDs with other fibrotic patterns	9.6	48.8 (10.3, 87.3)
Combined analysis*	**100**	**51.0 (39.1, 63.0)**

Relative effect of nintedanib vs placebo, % (95% CI)

*Test for heterogeneity: I^2=0%, τ^2=0, p=0.93.
Fixed and random effects meta-analyses were identical.

Conclusion

A meta-analysis of data from four placebo-controlled trials demonstrated that nintedanib approximately halved the rate of decline in FVC over 52 weeks across subjects with different forms of pulmonary fibrosis, with no evidence of heterogeneity in its relative treatment effect across patient populations

FVC, forced vital capacity. IPF, idiopathic pulmonary fibrosis. UIP, usual interstitial pneumonia.

The graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online. © The authors, CC-BY-NC-2022.
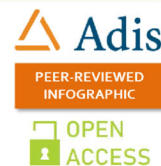
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Key Summary Points
Why carry out this study?
Decline in forced vital capacity (FVC) is variable both across interstitial lung diseases (ILDs) and among patients with the same ILD.
We investigated whether the effect of nintedanib on slowing decline in FVC was consistent across a spectrum of fibrosing ILDs.
What was learned from the study?
This meta-analysis of data from four placebo-controlled phase III trials showed that nintedanib had a consistent relative effect on reducing the rate of decline in FVC across subjects with different fibrosing ILDs.
These data show that nintedanib slows the progression of pulmonary fibrosis irrespective of the aetiology.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.19411025.

INTRODUCTION

The ILDs are a heterogeneous group of diffuse parenchymal lung disorders that may manifest as pulmonary fibrosis [1]. Pulmonary fibrosis may become progressive. Idiopathic pulmonary fibrosis (IPF) is often viewed as the "prototypic" progressive fibrosing ILD, but patients with other chronic ILDs may also develop a progressive fibrosing phenotype, characterised by increasing fibrotic abnormalities on high-resolution computed tomography (HRCT), decline in lung function, worsening symptoms and quality of life, and early mortality [2–6]. The course of fibrosing ILD is variable both across ILDs and among patients with the same ILD [7–10]. Decline in forced vital capacity (FVC) reflects the progression of ILD and has been associated with mortality in studies in several ILDs [4, 11–14].

Nintedanib is an intracellular inhibitor of tyrosine kinases with anti-inflammatory and anti-fibrotic effects [15–17]. The effect of nintedanib on slowing the rate of decline in FVC has been investigated in randomized placebo-controlled trials in subjects with IPF [18–21], fibrosing ILDs other than IPF that had progressed despite management deemed appropriate in clinical practice [20, 23], and ILD associated with systemic sclerosis (SSc-ILD) [24]. In this analysis, we assessed the consistency of the effect of nintedanib on the rate of decline in FVC (mL/year) over 52 weeks across four placebo-controlled phase III trials in subjects with different forms of pulmonary fibrosis.

METHODS

We used data on FVC decline from the INPULSIS trials (INPULSIS-1 and INPULSIS-2) in subjects with IPF [19], the SENSCIS trial in subjects with SSc-ILD [24] and the INBUILD trial in subjects with progressive fibrosing ILDs other than IPF [22] (Table 1). The INPULSIS, SENSCIS and INBUILD trials were carried out in compliance with the protocol and with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Conference on Harmonisation. The trials were approved by the local authorities. All subjects provided written informed consent prior to their participation.

The designs of the INPULSIS, SENSCIS and INBUILD trials have been published and the protocols are publicly available [19, 22, 24]. Briefly, subjects in the INPULSIS trials had IPF, FVC at least 50% predicted and diffusing capacity of the lungs for carbon monoxide

Table 1 Key inclusion criteria for the INPULSIS, SENSCIS and INBUILD trials

INPULSIS trials [19]	SENSCIS trial [24]	INBUILD trial [22]
Age ≥ 40 years	Age ≥ 18 years	Age ≥ 18 years
Diagnosis of IPF based on 2011 ATS/ERS/JRS/ALAT guidelines [43]	Diagnosis of SSc based on ACR/EULAR 2013 classification criteria [44] with first non-Raynaud symptom in prior ≤ 7 years	Clinical diagnosis of diffuse fibrosing ILD other than IPF
Fibrotic pattern on HRCT consistent with UIP	Predominant features on HRCT consistent with SSc-ILD	Reticulation with traction bronchiectasis (with or without honeycombing) on HRCT
FVC ≥ 50% predicted	Fibrotic ILD of ≥ 10% extent on HRCT	Progressive ILD defined by worsening in lung function, symptoms and/or imaging
DLco 30–79% predicted	FVC ≥ 40% predicted	Fibrotic ILD of ≥ 10% extent on HRCT
	DLco 30–89% predicted	FVC ≥ 45% predicted
		DLco 30–80% predicted

IPF idiopathic pulmonary fibrosis, *ATS* American Thoracic Society, *ERS* European Respiratory Society, *JRS* Japanese Respiratory Society, *ALATHRCT* high-resolution computed tomography, *FVC* forced vital capacity, *DLco* diffusing capacity of the lungs for carbon monoxide, *SSc* systemic sclerosis, *EULAR* European League Against Rheumatism, *ACR* American College of Rheumatology

(DLco) 30–79% predicted. Subjects in the SENSCIS trial had SSc with first non-Raynaud symptom in the prior 7 years or less, extent of fibrotic ILD on HRCT of at least 10%, FVC at least 40% predicted and DLco 30–89% predicted. Patients on prednisone dose of at most 10 mg/day or equivalent and/or stable therapy

with mycophenolate or methotrexate for at least 6 months were allowed to participate. Subjects in the INBUILD trial had a chronic fibrosing ILD other than IPF of at least 10% extent on HRCT, met criteria for ILD progression within the previous 2 years despite management deemed appropriate in clinical practice, and had FVC at least 45% predicted and DLco 30–80% predicted; the protocol excluded patients taking azathioprine, cyclosporine, mycophenolate, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids at a dose of more than 20 mg/day. Since the presence of an usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT has been associated with a faster rate of disease progression in studies in several ILDs [3, 25, 26], we also analysed the effect of nintedanib on the rate of decline in FVC in the INBUILD trial in subjects with a UIP-like fibrotic pattern on HRCT (defined in [22]) and in subjects with other fibrotic patterns on HRCT.

In every trial, the primary endpoint was the rate of decline in FVC (mL/year) assessed over 52 weeks using a random coefficient regression model (with random slopes and intercepts). The model assumed that data were missing at random. Missing data were not imputed. We performed fixed effect and random effects meta-analyses, based on the relative treatment effect (%) of nintedanib versus placebo on the rate of decline in FVC (mL/year) over 52 weeks. For each population, the relative treatment effect was calculated as the absolute treatment effect (and related standard error) normalised by the adjusted rate of decline in FVC (mL/year) in the placebo group to account for differences in natural history across ILDs. Heterogeneity of the relative treatment effect of nintedanib across populations was assessed using the I^2 statistic, τ^2 and corresponding p value from a Q test for heterogeneity.

RESULTS

The baseline characteristics of subjects treated in the INPULSIS, SENSCIS and INBUILD trials have been published [19, 22, 24] and are summarised in Table 2. Over 52 weeks, nintedanib

Table 2 Baseline characteristics of subjects in clinical trials of nintedanib

	INPULSIS-1 ($n = 513$)	INPULSIS-2 ($n = 548$)	SENSCIS ($n = 576$)	INBUILD: UIP-like fibrotic pattern on HRCT ($n = 412$)	INBUILD: other fibrotic patterns on HRCT ($n = 251$)
Male, n (%)	414 (80.7)	427 (77.9)	143 (24.8)	247 (60.0)	109 (43.4)
Age, years	66.9 (8.3)	66.6 (7.8)	54.0 (12.2)	68.0 (8.4)	62.1 (10.7)
Former or current smoker, n (%)	391 (76.2)	374 (68.2)	–	236 (57.3)	102 (40.6)
FVC mL	2792 (771)	2651 (780)	2500 (777)	2369 (741)	2268 (719)
FVC % predicted	79.9 (17.1)	79.2 (18.5)	72.5 (16.7)	70.6 (15.9)	66.4 (14.8)
DLco % predicted	47.7 (12.1)	46.8 (14.6)	53.0 (15.1)	46.6 (14.3)	45.4 (12.4)

Data are mean (SD) unless otherwise stated

HRCT high-resolution computed tomography, *FVC* forced vital capacity, *DLco* diffusing capacity of the lungs for carbon monoxide, *UIP* usual interstitial pneumonia

significantly reduced the rate of decline in FVC versus placebo in all the populations studied. The between-group absolute differences in the rate of decline in FVC were 125.3 mL/year (95% CI 77.7, 172.8) in INPULSIS-1, 93.7 mL/year (95% CI 44.8, 142.7) in INPULSIS-2, 41.0 mL/year (95% CI 2.9, 79.0) in SENSCIS and 107.0 mL/year (95% CI 65.4, 148.5) in INBUILD (128.2 mL/year [95% CI 70.8, 185.6] in subjects with a UIP-like fibrotic pattern on HRCT and 75.3 mL/year [95% CI 15.5, 135.0] in subjects with other fibrotic patterns on HRCT).

The relative effect of nintedanib versus placebo on the rate of decline in FVC ranged from 44% in SENSCIS to 61% in subjects with a UIP-like fibrotic pattern on HRCT in INBUILD (Fig. 1). There was no evidence of heterogeneity in the relative treatment effect of nintedanib across the patient populations studied ($I^2 = 0\%$, $\tau^2 = 0$, $p = 0.93$). In the combined analysis, which comprised 1257 subjects in the nintedanib group and 1042 subjects in the placebo group, nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks by 51.0% (95% CI 39.1, 63.0). The relative effect (95% CI) was the same using the fixed effect and random effects models.

DISCUSSION

We conducted a meta-analysis of the effect of nintedanib on the rate of decline in FVC based on data from over 2000 subjects with pulmonary fibrosis. We found that the relative effect of nintedanib on slowing the rate of FVC decline was consistent across patients with different types of ILD, with a relative reduction of approximately 50% across populations. The rate of FVC decline differed across the populations studied [19, 22, 24], leading to differences in the absolute effect of nintedanib that may be of clinical relevance, for example, in the impact of the same relative reduction in the rate of FVC decline on the risk of mortality. However, of note, the absolute rate of FVC decline observed in patients with IPF was similar to that observed in patients with other progressive fibrosing ILDs [14].

The pathobiology of progressive fibrosing ILD remains incompletely understood [27], but these findings support the proposition that fibrosing ILDs show commonalities in the pathobiological pathways that lead to progression of fibrosis [14, 27–30] and that nintedanib slows the progression of pulmonary fibrosis
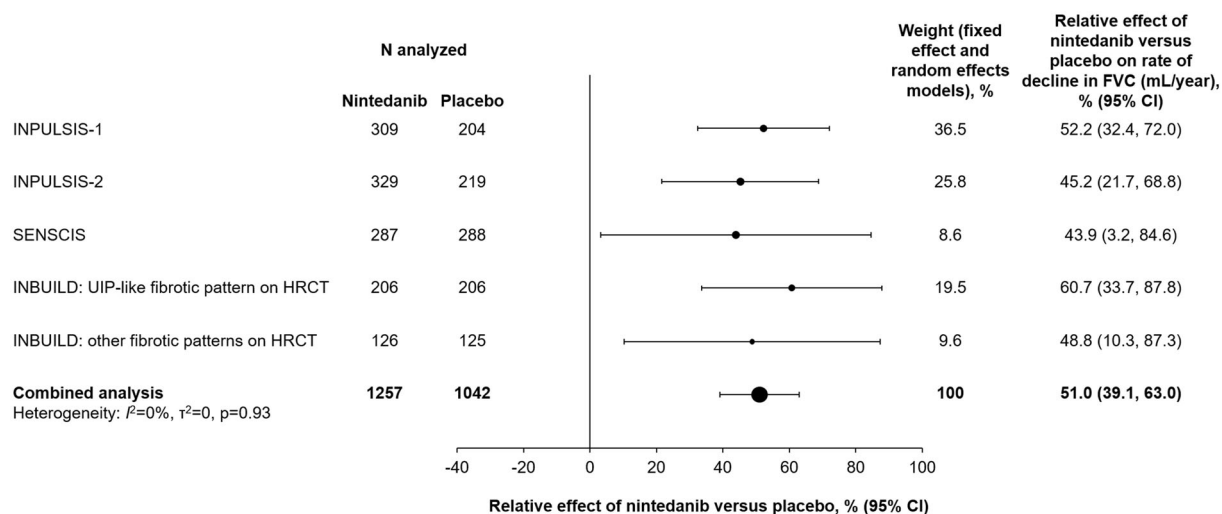
Fig. 1 Relative effect of nintedanib versus placebo on the rate of decline in FVC (mL/year) over 52 weeks in the INPULSIS, SENSCIS and INBUILD trials

irrespective of its aetiology [14, 17, 29–31]. Further support for this hypothesis is provided by subgroup analyses of data from the INBUILD trial that suggested that the effect of nintedanib on FVC decline was consistent irrespective of the underlying diagnosis [29, 30]. Subgroup analyses have also shown that nintedanib has a consistent effect on reducing FVC decline in subjects of different ages and disease severities based on FVC, DLco, or staging systems such as the composite physiologic index or GAP index [32–37].

These findings should not undermine the importance of determining an accurate diagnosis in patients with ILDs to ensure that individual patients can receive the appropriate care. Rather these data emphasise the importance of rigorous follow-up and prompt identification of disease progression in patients with fibrosing ILDs so that therapy that targets fibrosis can be initiated in a timely manner to slow further loss of lung function. Such close monitoring should involve regular assessment of pulmonary function and symptoms, and, when required, HRCT [38–40]. In the absence of clinical practice guidelines for fibrosing ILDs other than IPF, the management of patients with ILDs requires an individualised and multidisciplinary approach, including input from an expert pulmonologist.

Prompt initiation or escalation of therapy in patients with progressive fibrosis is needed to improve outcomes [38–40].

Our analyses have some limitations. The data on FVC decline were collected over a follow-up period of only 52 weeks. The data collected did not allow analyses to be conducted of the effects of nintedanib in patients with specific rare ILDs, or in patients taking particular immunomodulatory medications. However, previous analyses have demonstrated that nintedanib had a consistent effect on reducing FVC decline between subgroups based on use of immunomodulatory therapies in the INBUILD trial [41], and between subgroups based on use of a stable dose of mycophenolate for at least 6 months in patients with SSc-ILD in the SENSCIS trial [42].

CONCLUSION

A meta-analysis of data from four phase III clinical trials showed that despite differences in the rate of FVC decline across fibrosing ILDs, nintedanib approximately halved the rate of FVC decline over 52 weeks across the spectrum of pulmonary fibrosis.

ACKNOWLEDGEMENTS

REFERENCES

1. Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. N Engl J Med. 2020;383:958–68.

2. Hyldgaard C, Bendstrup E, Wells AU, Hilberg O. Unclassifiable interstitial lung diseases: clinical characteristics and survival. Respirology. 2017;22: 494–500.

3. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol. 2017;69:542–9.

4. Doubková M, Švancara J, Svoboda M, et al. EMPIRE Registry, Czech part: impact of demographics, pulmonary function and HRCT on survival and clinical course in idiopathic pulmonary fibrosis. Clin Respir J. 2018;12:1526–35.

5. Hoffmann-Vold AM, Fretheim H, Halse AK, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. Am J Respir Crit Care Med. 2019;200:1258–66.

6. Nasser M, Larrieu S, Si-Mohamed S, et al. Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study). Eur Respir J. 2021;57: 2002718.

7. Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest. 2014;145:723–8.

8. Oldham JM, Adegunsoye A, Valenzi E, et al. Characterisation of patients with interstitial pneumonia with autoimmune features. Eur Respir J. 2016;47: 1767–75.

9. Krauss E, El-Guelai M, Pons-Kuehnemann J, et al. Clinical and functional characteristics of patients with unclassifiable interstitial lung disease (uILD): long-term follow-up data from European IPF Registry (eurIPFreg). J Clin Med. 2020;9:2499.

10. Hoffmann-Vold AM, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis. 2021;80: 219–27.

11. Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2016;47: 588–96.

12. Gimenez A, Storrer K, Kuranishi L, Soares MR, Ferreira RG, Pereira CAC. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. Thorax. 2018;73:391–2.

13. Goh NS, Hoyles RK, Denton CP, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol. 2017;69: 1670–8.

14. Brown KK, Martinez FJ, Walsh SLF, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J. 2020;55:2000085.

15. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther. 2014;349:209–20.

16. Wollin L, Wex E, Pautsch A, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J. 2015;45:1434–45.

17. Wollin L, Distler JHW, Redente EF, et al. Potential of nintedanib in treatment of progressive fibrosing interstitial lung diseases. Eur Respir J. 2019;54: 1900161.

18. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365:1079–87.

19. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.

20. Maher TM, Stowasser S, Nishioka Y, et al. Biomarkers of extracellular matrix turnover in patients with idiopathic pulmonary fibrosis given nintedanib (INMARK study): a randomised, placebo-controlled study. Lancet Respir Med. 2019;7:771–9.

21. Lancaster L, Goldin J, Trampisch M, et al. Effects of nintedanib on quantitative lung fibrosis score in idiopathic pulmonary fibrosis. Open Respir Med J. 2020;14:22–31.

22. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381:1718–27.

23. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. Eur Respir J. 2021;59:2004538.

24. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med. 2019;380:2518–28.

25. Ryerson CJ, Urbania TH, Richeldi L, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. Eur Respir J. 2013;42:750–7.

26. Chan C, Ryerson CJ, Dunne JV, Wilcox PG. Demographic and clinical predictors of progression and mortality in connective tissue disease-associated interstitial lung disease: a retrospective cohort study. BMC Pulm Med. 2019;19:192.

27. Selman M, Pardo A. When things go wrong: exploring possible mechanisms driving the progressive fibrosis phenotype in interstitial lung diseases. Eur Respir J. 2021;58:2004507.

28. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ, IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J. 2018;51:1800692.

29. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020;8:453–60.

30. Matteson E, Kelly C, Distler JHW, et al. Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: subgroup analysis of the INBUILD trial. Arthritis Rheumatol. 2022. https://doi.org/10.1002/art.42075.

31. Ackermann M, Kim YO, Wagner WL, et al. Effects of nintedanib on the microvascular architecture in a lung fibrosis model. Angiogenesis. 2017;20:359–72.

32. Costabel U, Inoue Y, Richeldi L, et al. Efficacy of nintedanib in idiopathic pulmonary fibrosis across prespecified subgroups in INPULSIS. Am J Respir Crit Care Med. 2016;193:178–85.

33. Kolb M, Richeldi L, Behr J, et al. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. Thorax. 2017;72:340–6.

34. Brown KK, Flaherty KR, Cottin V, et al. Lung function outcomes in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. Respir Med. 2019;146:42–8.

35. Ryerson CJ, Kolb M, Richeldi L, et al. Effects of nintedanib in patients with idiopathic pulmonary fibrosis by GAP stage. ERJ Open Res. 2019;5:00127–2018.

36. Richeldi L, Kolb M, Jouneau S, et al. Efficacy and safety of nintedanib in patients with advanced idiopathic pulmonary fibrosis. BMC Pulm Med. 2020;20:3.

37. Glaspole I, Bonella F, Bargagli E, et al. Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis who are elderly or have comorbidities. Respir Res. 2021;22:125.

38. George PM, Spagnolo P, Kreuter M, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med. 2020;8:925–34.

39. Hoffmann-Vold AM, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatol. 2020;2:E71–83.

40. Nambiar AM, Walker CM, Sparks JA. Monitoring and management of fibrosing interstitial lung diseases: a narrative review for practicing clinicians. Ther Adv Respir Dis. 2021;15:17534666211039772.

41. Cottin V, Richeldi L, Rosas I, et al. Nintedanib and immunomodulatory therapies in progressive fibrosing interstitial lung diseases. Respir Res. 2021;22:84.

42. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: subgroup analysis of the SENSCIS trial. Lancet Respir Med. 2021;9:96–106.

43. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.

44. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2013;72:1747–55.