Consistent effect of nintedanib on reducing FVC decline across interstitial lung diseases (ILDs)

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Introduction

- In patients with chronic fibrosing ILDs and a progressive phenotype, decline in forced vital capacity (FVC) is associated with mortality.[1-4]
- Based on the hypothesis that there are pathophysiological similarities across fibrosing ILDs with different aetiologies and rates of progression, the effect of nintedanib on the rate of decline in FVC has been investigated in patients with a spectrum of fibrosing ILDs.

Aim

- To assess the consistency of the effect of nintedanib versus placebo on the rate of decline in FVC across clinical trials in subjects with various fibrosing ILDs.

Methods

- The effects of nintedanib were investigated in Phase III placebo-controlled trials in subjects with idiopathic pulmonary fibrosis (IPF) (INPULSIS-1 and -2),[5] systemic sclerosis-associated ILD (SSc-ILD) (SENSCIS)[6] and progressive fibrosing ILDs other than IPF (INBUILD).[7]

Key inclusion criteria for INPULSIS, SENSCIS and INBUILD trials

INPULSIS trials[5]	SENSCIS trial[6]	INBUILD trial[7]
▪ Age ≥40 years ▪ Diagnosis of IPF based on 2011 ATS/ERS/JRS/ALAT guidelines[8] ▪ Fibrotic pattern on HRCT consistent with UIP ▪ FVC ≥50% predicted ▪ DLco 30-80% predicted	▪ Age ≥18 years ▪ Diagnosis of SSc based on ACR / EULAR 2013 classification criteria[9] with first non-Raynaud symptom ≤7 years before screening ▪ Predominant features on HRCT consistent with SSc-ILD ▪ Fibrotic ILD of ≥10% extent on HRCT ▪ FVC ≥40% predicted ▪ DLco 30–89% predicted	▪ Age ≥18 years ▪ Clinical diagnosis of diffuse fibrosing ILD other than IPF ▪ Reticulation with traction bronchiectasis (with or without honeycombing) on HRCT ▪ Progressive ILD defined by worsening in lung function, symptoms, or imaging ▪ Fibrotic ILD of ≥10% extent on HRCT ▪ FVC ≥45% predicted ▪ DLco 30-80% predicted

UIP, usual interstitial pneumonia.

- In each trial, the primary endpoint was the annual rate of decline in FVC (mL/year) assessed over 52 weeks.[5-7]
- We performed fixed effect and random effects meta-analyses, based on the relative treatment effects (%) of nintedanib versus placebo on the rate of decline in FVC (mL/year) over 52 weeks, to account for the different natural histories of the ILDs. In each trial, 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.

Results

Baseline characteristics of subjects in clinical trials of nintedanib

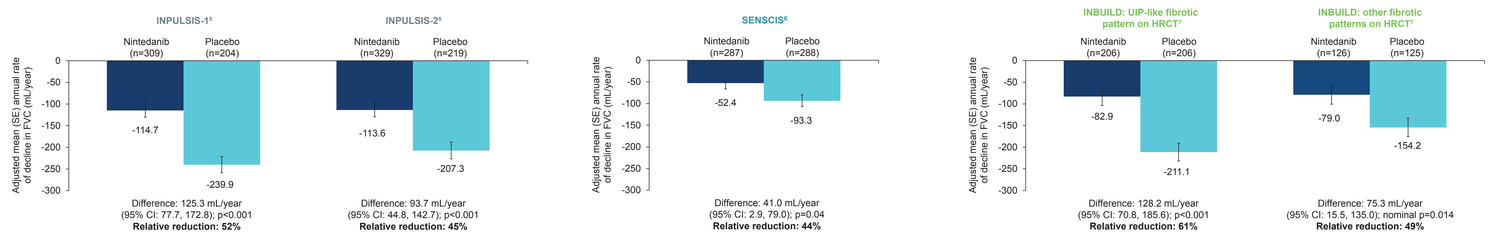
	INPULSIS-1 (n=513)	INPULSIS-2 (n=548)	SENSCIS (n=576)	INBUILD: UIP-like fibrotic pattern on HRCT (n=412)	INBUILD: other fibrotic patterns on HRCT (n=251)*
Male (%)	80.7	77.9	24.8	60.0	43.4
Age (years)	66.9 (8.3)	66.6 (7.8)	54.0 (12.2)	68.0 (8.4)	62.1 (10.7)
Former or current smoker (%)	76.2	68.2	-	57.3	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)

Mean (SD) or % of subjects.
*The following co-existing features were accepted: ground glass opacity, upper lung or peribronchovascular predominance, mosaic attenuation, air trapping, centrilobular nodules.

Rate of decline in FVC over 52 weeks

- Nintedanib significantly reduced the rate of decline in FVC (mL/year) over 52 weeks versus placebo in the INPULSIS, SENSCIS and INBUILD trials (Figure 1).

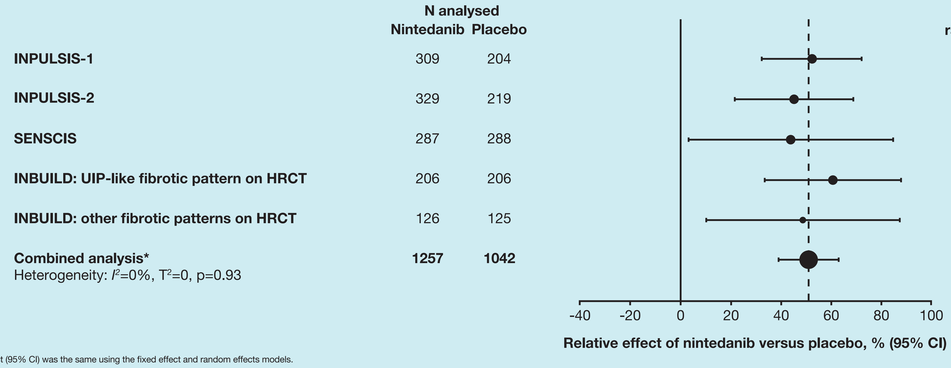
Figure 1. Rate of decline in FVC (mL/year) over 52 weeks in the INPULSIS, SENSCIS and INBUILD trials



Meta-analysis of effect of nintedanib versus placebo on rate of decline in FVC over 52 weeks

- Nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks versus placebo in the combined analysis by 51.0% (95% CI 39.1, 63.0). The effect of nintedanib was consistent across the trials in different ILDs, with no evidence of heterogeneity (p=0.93) (Figure 2).

Figure 2. 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



*Relative effect (95% CI) was the same using the fixed effect and random effects models.

Conclusion

- **Despite differences in the rate of lung function decline in the placebo groups, nintedanib had a consistent relative treatment effect on reducing the rate of decline in FVC over 52 weeks across the spectrum of fibrosing ILDs.**

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