Safety and tolerability of nintedanib in patients with fibrosing interstitial lung diseases (ILDs): pooled data from four trials

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INTRODUCTION

- The effects of nintedanib have been investigated in placebo-controlled trials in patients with idiopathic pulmonary fibrosis (IPF),[1] progressive fibrosing ILDs other than IPF,[2] and ILD associated with systemic sclerosis (SSc-ILD).[3]
- In all these trials, nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks, with side-effects that were manageable for most patients.[1-3]

AIM

- To characterise the safety and tolerability of nintedanib in patients with fibrosing ILDs using pooled data from four clinical trials.

METHODS

- Data were pooled from the Phase III INPULSIS-1 and -2, INBUILD and SENSCIS trials.

Key inclusion criteria

INPULSIS trials[1]	INBUILD trial[2]	SENSCIS trial[3]
▪ Age ≥40 years ▪ Diagnosis of IPF based on 2011 ATS/ERS/JRS/ALAT guidelines[4] ▪ Fibrotic pattern on HRCT consistent with usual interstitial pneumonia (UIP) ▪ FVC ≥50% predicted ▪ DLco 30–79% predicted	▪ Age ≥18 years ▪ Clinical diagnosis of diffuse fibrosing ILD other than IPF ▪ Reticulation with traction bronchiectasis (with or without honey-combing) 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	▪ Age ≥18 years ▪ Diagnosis of SSc based on ACR/EULAR 2013 classification criteria[5] 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

- In each trial, subjects were randomised to receive nintedanib 150 mg bid or placebo. Dose reductions to 100 mg bid and treatment interruptions were allowed to manage adverse events.
- Adverse events were reported by the investigators irrespective of causality and were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. All adverse events reported over 52 weeks (or until 28 days after last trial drug intake in patients who discontinued trial drug before week 52) were analysed.
- Based on the mechanism of action of nintedanib, major adverse cardiovascular events (MACE), myocardial infarction, bleeding, and hepatic adverse events were considered of particular interest.

CONCLUSIONS

- In clinical trials in patients with progressive fibrosing ILDs, the adverse events associated with nintedanib were manageable for most patients.
- Gastrointestinal adverse events, particularly diarrhoea, were the most frequent adverse events associated with nintedanib, but were managed without treatment discontinuation in most patients.

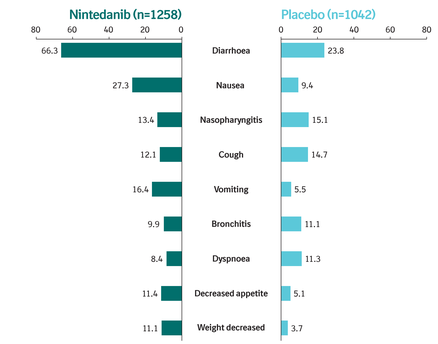
RESULTS

Baseline characteristics

	Nintedanib (n=1258)	Placebo (n=1042)
Mean (SD) age, years	63.5 (10.7)	63.0 (11.6)
Male, %	59.9	56.3
Mean (SD) body mass index, kg/m²	27.6 (4.8)	27.4 (5.1)
Mean (SD) time since diagnosis of ILD, years	2.4 (2.4)	2.6 (2.6)
Current or former smoker, %	50.3	45.1
Mean (SD) FVC % predicted	75.1 (17.7)	74.3 (17.4)
Mean (SD) DLco % predicted	47.9 (13.8)	49.0 (14.6)

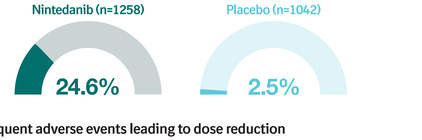
- Mean (SD) exposure to nintedanib was 10.3 (3.5) months. Mean (SD) exposure to placebo was 11.1 (2.7) months.

Most frequent adverse events

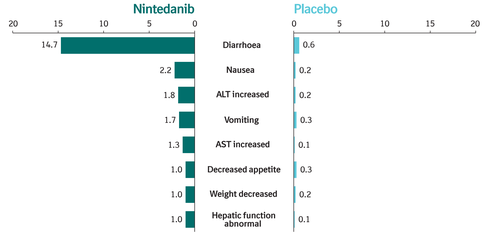


Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Data are % of patients with ≥1 such adverse event. Adverse events reported in >10% of patients in the nintedanib or placebo group are shown.

Adverse events leading to dose reduction



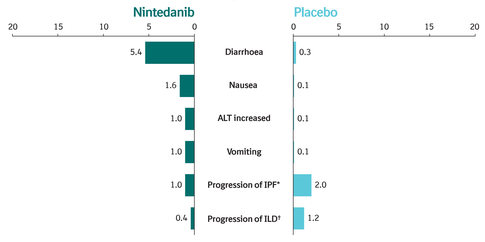
Most frequent adverse events leading to dose reduction



Adverse events were coded according to preferred terms in the MedDRA. Data are % of patients with ≥1 such adverse event reported over 52 weeks. Adverse events leading to dose reduction in ≥1% of patients in the nintedanib or placebo group are shown. Only permanent dose reductions were considered, except for the INBUILD trial where all dose reductions were considered.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Adverse events leading to treatment discontinuation

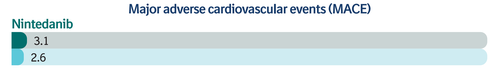
Most frequent adverse events leading to treatment discontinuation



Adverse events were coded according to preferred terms in the MedDRA. Data are % of patients with ≥1 such adverse event.
Adverse events leading to treatment discontinuation in ≥1% of patients in either nintedanib or placebo group are shown. ALT, alanine aminotransferase.
*MedDRA preferred term 'IPF'. †MedDRA preferred term 'ILD'.

Adverse events of interest

Major adverse cardiovascular events (MACE)

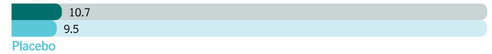


Based on fatal adverse events in MedDRA system organ classes "cardiac disorders" and "vascular disorders"; any fatal and non-fatal events in the subordinate standardised MedDRA query "myocardial infarction" (broad definition); any fatal and non-fatal stroke events (based on selected preferred terms); and the MedDRA preferred terms "sudden death", "cardiac death" and "sudden cardiac death".

Myocardial infarction

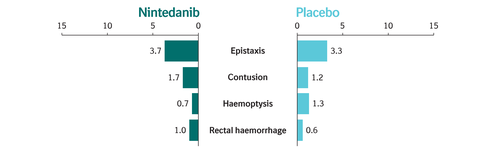
Based on narrow standardised MedDRA query "myocardial infarction".

Bleeding adverse events



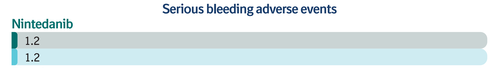
Based on standardised MedDRA query "haemorrhage terms (excluding laboratory terms)" (narrow definition).

Most frequent bleeding adverse events



Based on MedDRA preferred terms included in standardised MedDRA query "haemorrhage terms (excluding laboratory terms)" (narrow definition). Adverse events reported in ≥1% of patients in the nintedanib or placebo group are shown.

Serious bleeding adverse events



Based on standardised MedDRA query "haemorrhage terms (excluding laboratory terms)" (narrow definition). Serious adverse events were defined as events that resulted in death, were life threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed serious for any other reason.

Hepatic adverse events

Based on standardised MedDRA query "liver related investigations, signs and symptoms" (broad definition).

Elevations in ALT and/or AST ≥3×ULN

ULN, upper limit of normal. ALT, alanine aminotransferase. AST, aspartate aminotransferase.
Two patients in the placebo group and one in the nintedanib group had elevations in ALT and/or AST ≥3×ULN and elevation in bilirubin ≥2×ULN.

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REFERENCES
1. Richeldi L et al. N Engl J Med 2014;370:2071–2082.
2. Flaherty KR et al. N Engl J Med 2019;381:1718–1727.
3. Distler O et al. N Engl J Med 2019;380:2518–2528.
4. Raghu G et al. Am J Respir Crit Care Med 2011;183:788–824.
5. van den Hoogen F et al. Ann Rheum Dis 2013;72:1747–1755.

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