Effects of nintedanib in patients with progressive fibrosing interstitial lung diseases (ILDs) by composite physiologic index (CPI)

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INTRODUCTION

- In the INBUILD trial in patients with progressive fibrosing ILDs other than idiopathic pulmonary fibrosis (IPF), nintedanib slowed the rate of decline in FVC (mL/year) over 52 weeks by 57% compared with placebo, with adverse events that were manageable for most patients.[1]
- The Composite Physiologic Index (CPI), a measure of the severity of pulmonary fibrosis, was developed in patients with IPF.[2] Higher scores on the CPI have been associated with mortality in patients with various ILDs.[2-6]

AIM

- To evaluate the efficacy and safety of nintedanib in subgroups by CPI at baseline in the INBUILD trial.

METHODS

Trial design[1]

- Patients in the INBUILD trial had diffuse fibrosing ILD (reticular abnormality with traction bronchiectasis, with or without honeycombing) of >10% extent on HRCT, FVC ≥45% predicted, and DLco ≥30%–<80% predicted. Patients with IPF were excluded.
- Patients met ≥1 of the following criteria for ILD progression at any time within the 24 months before screening, despite management deemed appropriate in clinical practice:

- Patients were randomized to receive nintedanib or placebo, stratified by HRCT pattern (usual interstitial pneumonia [UIP]-like fibrotic pattern or other fibrotic patterns).
- The primary endpoint was the rate of decline in FVC (mL/year) over 52 weeks. Patients continued to receive blinded randomized treatment until all subjects had completed the follow-up visit or entered the open-label extension study (INBUILD-ON).

Analyses

The CPI is calculated using the formula: **91.0 − (0.65 × DLco % predicted) − (0.53 × FVC % predicted) + (0.34 × FEV_1 % predicted)**.[2]

- In subgroups by CPI ≤45 versus >45 at baseline, we analyzed *post-hoc* the rate of FVC decline (mL/year) over 52 weeks and the time to absolute decline in FVC ≥10% predicted or death over the whole INBUILD trial in the overall population and in patients with a UIP-like fibrotic pattern on HRCT.
- Interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib versus placebo between subgroups. No adjustment for multiplicity was made.

CONCLUSIONS

- In the INBUILD trial, nintedanib had a consistent effect on slowing the progression of ILD in patients with progressive fibrosing ILDs across subgroups by CPI at baseline, with adverse events that were manageable for most patients.

RESULTS

Patients

202 (30.9%) had CPI ≤45 — 452 (69.1%) had CPI >45

CPI could not be calculated in 9 patients due to missing values.

Baseline characteristics

Overall population CPI ≤45 (n=202)	Overall population CPI >45 (n=452)		Patients with a UIP-like fibrotic pattern on HRCT CPI ≤45 (n=131)	Patients with a UIP-like fibrotic pattern on HRCT CPI >45 (n=277)
64.7	66.3	Mean age (years)	67.3	68.3
49.0	44.7	Female, %	44.3	37.9
52.0	51.1	Former or current smoker, %	57.3	58.1
81.0	63.5	Mean FVC % predicted	83.1	64.5
61.5	39.2	Mean DLco % predicted	62.1	39.2

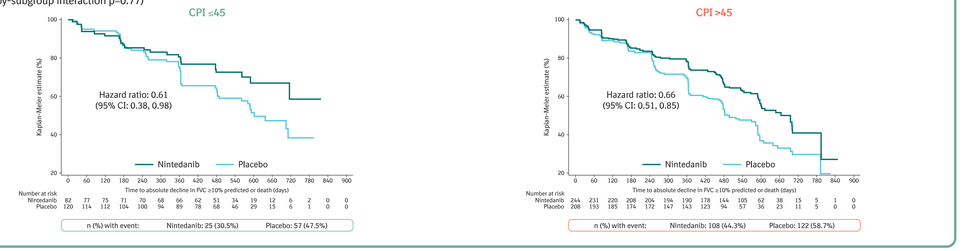
Rate of decline in FVC (mL/year) over 52 weeks

- In both the placebo and nintedanib groups, the rate of FVC decline over 52 weeks was numerically greater in patients with CPI >45 than ≤45 at baseline. The interaction p-values did not indicate heterogeneity in the treatment effect of nintedanib versus placebo between the subgroups by CPI.

Rate of decline in FVC (mL/year) over 52 weeks in subgroups by CPI at baseline

Time to absolute decline in FVC ≥10% predicted or death in the overall population in subgroups by CPI at baseline

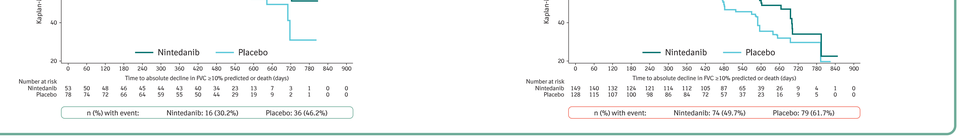
(treatment-by-subgroup interaction p=0.77)



n (%) with event: Nintedanib: 25 (30.5%) Placebo: 57 (47.5%) | Nintedanib: 108 (44.3%) Placebo: 122 (58.7%)

Time to absolute decline in FVC ≥10% predicted or death in patients with a UIP-like fibrotic pattern on HRCT in subgroups by CPI at baseline

(treatment-by-subgroup interaction p=0.66)

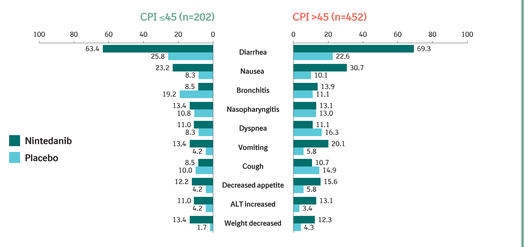


n (%) with event: Nintedanib: 16 (30.2%) Placebo: 36 (46.2%) | Nintedanib: 74 (49.7%) Placebo: 79 (61.7%)

Adverse events

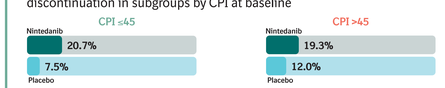
- The adverse event profile of nintedanib was generally consistent between the subgroups by CPI at baseline.

Adverse events (reported irrespective of causality) in subgroups by CPI at baseline



Adverse events were coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Data are % of patients with ≥1 such adverse event, reported over 52 weeks (or until 28 days after last trial drug intake in patients who discontinued trial drug before week 52). Adverse events reported in >12% of patients in either the nintedanib or placebo group in the total trial population are shown. ALT, alanine aminotransferase.

Proportions of patients with adverse events leading to treatment discontinuation in subgroups by CPI at baseline



Data are % of patients with ≥1 such adverse event, reported over 52 weeks.

Proportions of patients with serious adverse events in subgroups by CPI at baseline

Data are % of patients with ≥1 such adverse event reported over 52 weeks (or until 28 days after last trial drug intake in patients who discontinued trial drug before week 52). Serious adverse events were defined as events that resulted in death, were life-threatening, resulted in hospitalization or prolonged hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed serious for any other reason.

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