Effects of nintedanib on progression of ILD in patients with fibrosing ILDs and a progressive phenotype: further analyses of the INBUILD® trial

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Introduction

- In the INBUILD trial in subjects with chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (other than idiopathic pulmonary fibrosis [IPF]), nintedanib slowed the rate of decline in FVC (mL/year) over 52 weeks compared with placebo.[1]

Aim

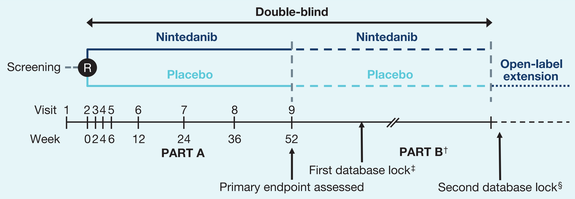
- To assess the effects of nintedanib on the progression of ILD over the whole INBUILD trial.

Methods

Trial design[1]

- Subjects had an ILD other than IPF, diagnosed according to the investigator's usual clinical practice; reticular abnormality with traction bronchiectasis (with or without honeycombing) of >10% extent on HRCT; FVC ≥45% predicted; DLco ≥30%–<80% predicted.
- Subjects met ≥1 of the following criteria for ILD progression in the 24 months before screening, despite management deemed appropriate in clinical practice:

- Subjects were randomised to receive nintedanib or placebo, stratified by fibrotic pattern on HRCT (usual interstitial pneumonia [UIP]-like fibrotic pattern or other fibrotic patterns), based on central review.
- For each subject, the trial consisted of two parts. Part A comprised 52 weeks of treatment. Part B was a variable treatment period beyond week 52 during which subjects continued to receive blinded randomised treatment until all subjects had completed the follow-up visit or entered the open-label extension study.



R, randomisation 1:1, stratified by HRCT pattern (UIP-like fibrotic pattern or other fibrotic patterns). †Visits occurred every 16 weeks until end of treatment. ‡After last subject had completed week 52 visit. §After all patients had completed follow-up visit or entered open-label extension study.

Analyses

- In pre-specified analyses, we assessed the following over the whole trial:
  - Time to death
  - Time to acute exacerbation of ILD or death
  - Time to ILD progression (absolute decline in FVC ≥10% predicted) or death.
- Analyses were based on a log-rank test and a Cox proportional hazards model was used to derive hazard ratios and 95% confidence intervals.
- Analyses were performed in both co-primary analysis populations: the overall population and subjects with a UIP-like fibrotic pattern on HRCT.
- Adverse events are presented descriptively.

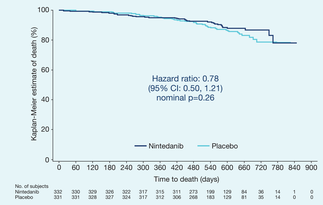
Results

- Among 663 subjects, mean (SD) age was 65.8 (9.8) years and FVC was 69.0 (15.6) % predicted. The most common ILD diagnoses were hypersensitivity pneumonitis (26.1%) and autoimmune ILDs (25.6%).[1]
- Median follow-up time for time-to-event endpoints was approximately 19 months.
- Mean (SD) exposure to trial medication was 15.6 (7.2) and 16.8 (5.8) months in the nintedanib and placebo groups, respectively.

Deaths

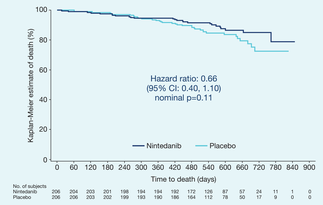
- In the overall population, the hazard ratio for death was 0.78, reflecting a risk reduction of 22% with nintedanib versus placebo. In subjects with a UIP-like fibrotic pattern on HRCT, a greater proportion of subjects in both treatment groups died and the risk reduction with nintedanib versus placebo was greater (hazard ratio: 0.66).

Time to death in overall population



n (%) who died: Nintedanib: 36 (10.8%) Placebo: 45 (13.6%)

Time to death in subjects with UIP-like fibrotic pattern on HRCT

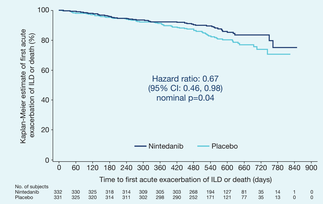


n (%) who died: Nintedanib: 25 (12.1%) Placebo: 36 (17.5%)

Acute exacerbation of ILD or death

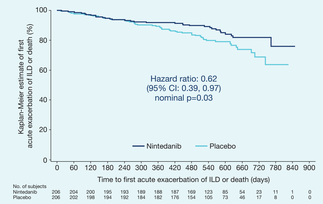
- In the overall population, the hazard ratio for first acute exacerbation of ILD or death was 0.67, reflecting a risk reduction of 33% with nintedanib versus placebo. In subjects with a UIP-like fibrotic pattern on HRCT, the hazard ratio was 0.62.

Time to first acute exacerbation of ILD or death in overall population



n (%) with event: Nintedanib: 46 (13.9%) Placebo: 65 (19.6%)

Time to first acute exacerbation of ILD or death in subjects with UIP-like fibrotic pattern on HRCT

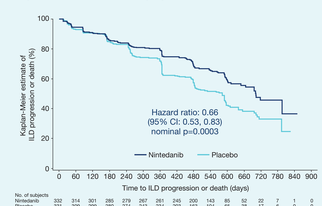


n (%) with event: Nintedanib: 31 (15.0%) Placebo: 47 (22.8%)

Progression of ILD (absolute decline in FVC ≥10% predicted) or death

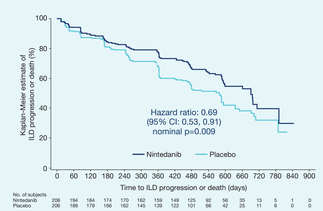
- In the overall population, the hazard ratio for progression of ILD or death was 0.66, reflecting a risk reduction of 34% with nintedanib versus placebo. The hazard ratio was similar in subjects with a UIP-like fibrotic pattern on HRCT (0.69).

Time to ILD progression (absolute decline in FVC ≥10% predicted) or death in overall population



n (%) with event: Nintedanib: 134 (40.4%) Placebo: 181 (54.7%)

Time to ILD progression (absolute decline in FVC ≥10% predicted) or death in subjects with UIP-like fibrotic pattern on HRCT)

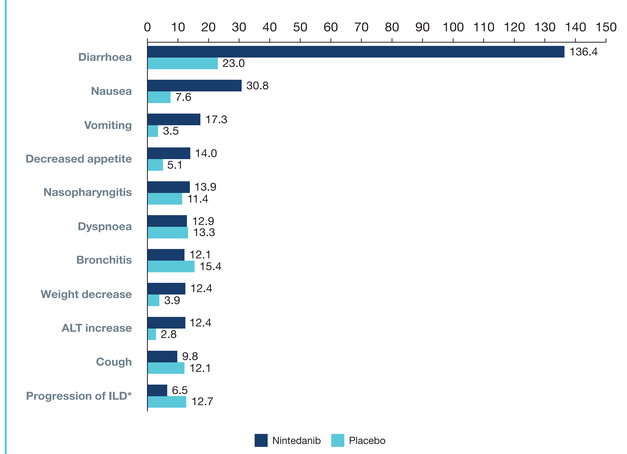


n (%) with event: Nintedanib: 90 (43.7%) Placebo: 115 (55.8%)

Adverse events

- The adverse event profile of nintedanib observed over the whole trial was consistent with that observed over 52 weeks.[1] No new safety signals were identified.

Most frequent adverse events (reported irrespective of causality)



Adverse events were reported between the first trial drug intake and 28 days after the last trial drug intake. Adverse events were coded based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events with an incidence rate of >12 events per 100 patient-years in either treatment group are shown. *Corresponded to the MedDRA preferred term "interstitial lung disease". ALT, alanine aminotransferase.

Conclusions

- **Analyses based on the whole INBUILD trial show that in patients with progressive fibrosing ILDs other than IPF:**
  - **events indicating further progression of ILD occurred frequently**
  - **nintedanib reduced the risk of clinically meaningful outcomes compared with placebo, with an adverse event profile consistent with that observed over the first 52 weeks.**

References

1. Flaherty KR et al. N Engl J Med 2019;381:1718–27.

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