Effect of nintedanib on decline in forced vital capacity (FVC) in patients with progressive fibrosing interstitial lung diseases (ILDs) by GAP stage

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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 GAP (gender, age, lung physiology) index and staging system was developed to estimate mortality risk in patients with IPF,[2] and has also shown utility in patients with other fibrosing ILDs.[3–6]

AIM

- To evaluate the efficacy and safety of nintedanib in subgroups by GAP stage 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 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

- In the GAP index and staging system, points are assigned based on sex, age, FVC % predicted, and DLco % predicted to obtain a total score (GAP index) ranging from 0 to 8.[2] Patients are classified as at GAP stage I (0–3 points), II (4–5 points) or III (6–8 points).
- In subgroups by GAP stage I versus II/III at baseline, we analyzed *post-hoc* the rate of FVC decline (mL/year) over 52 weeks and time to absolute decline from baseline in FVC ≥10% predicted or death over the whole 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 GAP stage at baseline, with adverse events that were manageable for most patients.

RESULTS

Patients

294 (44.3%) at GAP stage I — 369 (55.7%) at GAP stage II/III

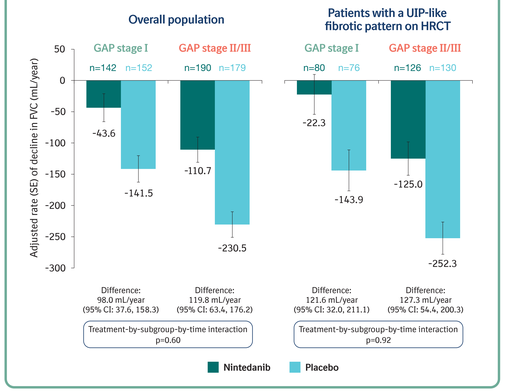
Baseline characteristics

Overall population			Patients with a UIP-like fibrotic pattern on HRCT	
GAP stage I (n=294)	GAP stage II/III (n=369)		GAP stage I (n=156)	GAP stage II/III (n=256)
60.6	69.8	Mean age (years)	63.0	71.0
66.3	30.4	Female, %	62.2	26.6
39.1	60.4	Former or current smoker, %	45.5	64.5
74.5	64.6	Mean FVC % predicted	77.8	66.2
53.6	40.3	Mean DLco % predicted	55.9	41.0

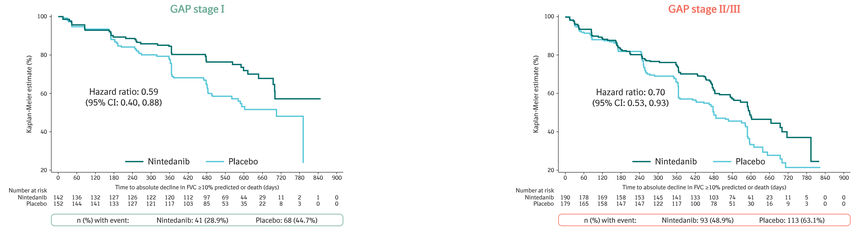
Rate of decline in FVC (mL/year) over 52 weeks

- In both the nintedanib and placebo groups, the rate of decline in FVC was numerically more pronounced in patients at GAP stage II/III than I. The interaction p-values did not indicate heterogeneity in the treatment effect of nintedanib versus placebo between the subgroups by GAP stage.

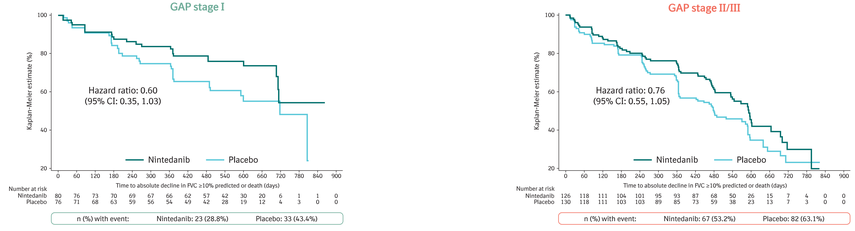
Rate of decline in FVC (mL/year) over 52 weeks in subgroups by GAP stage at baseline



Time to absolute decline in FVC ≥10% predicted or death in the overall population in subgroups by GAP stage at baseline
(treatment-by-subgroup interaction p=0.42)



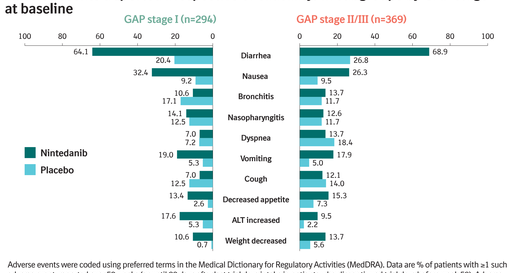
Time to absolute decline in FVC ≥10% predicted or death in patients with a UIP-like fibrotic pattern on HRCT in subgroups by GAP stage at baseline
(treatment-by-subgroup interaction p=0.36)



Adverse events

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

Adverse events (reported irrespective of causality) in subgroups by GAP stage 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 GAP stage 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 GAP stage 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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