Does nintedanib have the same effect on FVC decline in patients with progressive fibrosing ILDs treated with DMARDs or glucocorticoids?

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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 forced vital capacity (FVC) (mL/year) over 52 weeks by 57% versus placebo.[1]
- Subgroup analyses suggested that the effect of nintedanib on reducing the rate of decline in FVC was consistent across subgroups with different ILD diagnoses.[2]
- Autoimmune rheumatic diseases are commonly treated using disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids.

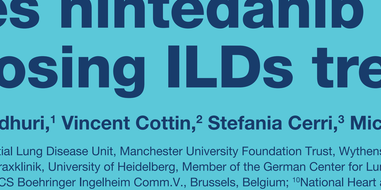
Aim

- To assess the influence of DMARDs and/or glucocorticoids at baseline on the effect of nintedanib in the INBUILD trial.

Methods

Trial design[1]

- Subjects in the INBUILD trial 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; diffusing capacity for carbon monoxide (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).
- Patients taking stable doses of medications to treat autoimmune rheumatic diseases were eligible to participate, but patients taking azathioprine; cyclosporine; mycophenolate mofetil, tacrolimus; oral glucocorticoids >20 mg/day; the combination of oral glucocorticoids, azathioprine and N-acetylcysteine; cyclophosphamide; or rituximab were not eligible.
  - Investigators were asked not to consider patients with autoimmune disease that was managed using any of these therapies for participation in the trial. Patients who took these therapies to treat their ILD, and whose ILD was progressing, could participate in the trial if the restricted therapy was discontinued.
  - Apart from the restricted therapies listed above, there was no limit on the use of stable doses of biologic or non-biologic DMARDs.
  - Initiation of the above therapies was allowed after 6 months of trial treatment in subjects with deterioration of ILD or autoimmune disease.

Analyses

- We assessed the rate of decline in FVC (mL/year) over 52 weeks in subgroups by use of DMARDs and/or glucocorticoids at baseline.
- DMARDs were identified based on the WHO standardised drug grouping (SDG) plus baricitinib and excluding denosumab. Glucocorticoids (with oral, intravenous [IV], IV bolus, IV drip, or intramuscular administration) were identified based on the WHO SDG.
- Interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib versus placebo across the subgroups. No adjustment for multiplicity was made.
- Adverse events are presented descriptively.

Results

At baseline, 382 subjects (57.6%) were taking DMARDs and/or glucocorticoids:

54.4% were taking glucocorticoids

Prednisone	25.6%
Prednisolone	19.9%
Methylprednisolone	5.1%
Meprednisone	1.4%
Deflazacort	0.9%

11.6% were taking non-biologic DMARDS

Hydroxychloroquine /sulphate	4.5%
Methotrexate	2.9%
Leflunomide	2.7%
Sulfasalazine	1.5%

3.3% were taking biologic DMARDS

Abatacept	0.9%

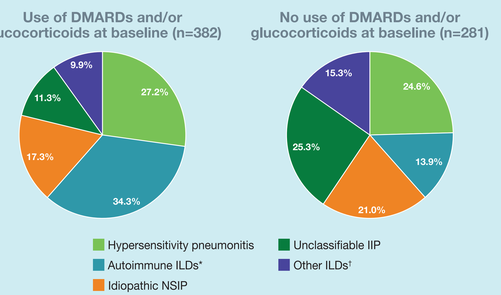
Therapies taken by ≥5 patients (0.8%) are shown.

Baseline characteristics of subgroups by use of DMARDs and/or glucocorticoids

DMARDs and/or glucocorticoids at baseline	Male (%)		Age (years)		UIP-like fibrotic pattern on HRCT (%)	
	Use	No use	Use	No use	Use	No use
	53.1	54.4	65.4	66.2	62.0	62.3
	FVC (mL)		FVC % predicted		DLco % predicted	
	2288	2388	67.5	71.0	45.0	47.7

Mean or % of subjects

ILD diagnoses in subgroups by use of DMARDs and/or glucocorticoids at baseline

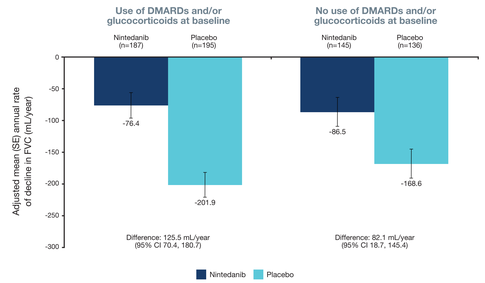


*Included rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, mixed connective tissue disease-associated ILD, plus subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of the case report form. †Included sarcoidosis, exposure-related ILDs and selected terms in the "Other fibrosing ILDs" category of the case report form. NSIP, non-specific interstitial pneumonia.

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

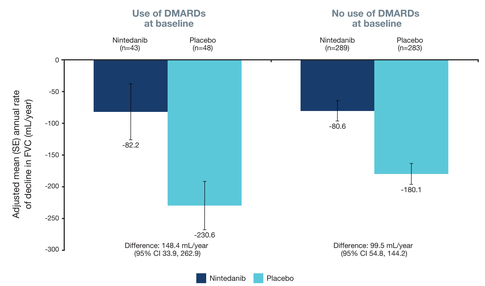
- In the placebo group, the rate of FVC decline was numerically greater in subjects who used DMARDs and/or glucocorticoids at baseline (Figure 1).
- Nintedanib reduced the rate of FVC decline versus placebo both in subjects who did and did not use DMARDs and/or glucocorticoids at baseline. The interaction p-value did not indicate a differential treatment effect of nintedanib between these subgroups (Figure 1).
- Similar results were observed in subgroups by use of DMARDs (only) and glucocorticoids (only) (Figures 2 and 3).

Figure 1. *Rate of decline in FVC (mL/year) over 52 weeks in subgroups by use of DMARDs and/or glucocorticoids at baseline*



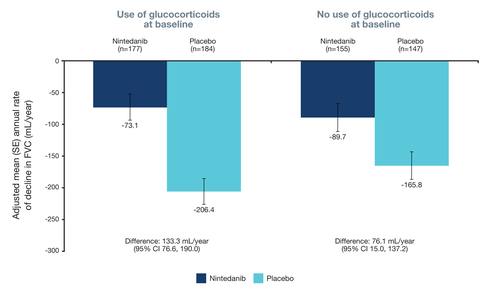
Treatment-by-subgroup-by time interaction p=0.31

Figure 2. *Rate of decline in FVC (mL/year) over 52 weeks in subgroups by use of DMARDs at baseline*



Treatment-by-subgroup-by time interaction p=0.44

Figure 3. *Rate of decline in FVC (mL/year) in subgroups by use of glucocorticoids at baseline*

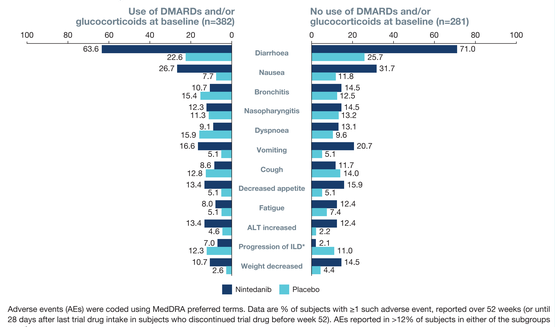


Treatment-by-subgroup-by time interaction p=0.18

Adverse events

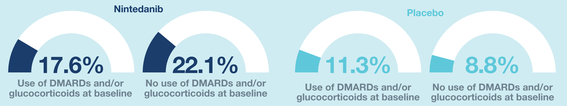
- The adverse event profile of nintedanib was generally consistent between subgroups by use of DMARDs and/or glucocorticoids at baseline (Figures 4 and 5).

Figure 4. *Most frequent adverse events (reported irrespective of causality) in subgroups by use of DMARDs and/or glucocorticoids at baseline*



Adverse events (AEs) were coded using MedDRA preferred terms. Data are % of subjects with ≥1 such adverse event, reported over 52 weeks (or until 28 days after last trial drug intake in subjects who discontinued trial drug before week 52). AEs reported in >12% of subjects in either of the subgroups are shown.
*Based on MedDRA preferred term "interstitial lung disease". ALT, alanine aminotransferase.

Figure 5. *Proportions of subjects with adverse events leading to discontinuation of trial drug*



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

Conclusions

- **In the INBUILD trial in subjects with progressive fibrosing ILDs, nintedanib had a consistent effect on reducing the rate of decline in FVC in subjects who did and did not use DMARDs and/or glucocorticoids at baseline.**
- **The adverse event profile of nintedanib was consistent between subgroups by use of DMARDs and/or glucocorticoids at baseline.**

References

1. Flaherty KR et al. N Engl J Med 2019;381:1718-27.
2. Wells AU et al. Lancet Respir Med 2020;8:453-60.

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