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Efficacy and safety of nintedanib in patients with autoimmune disease-related interstitial lung disease treated with DMARDs and/or glucocorticoids at baseline

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Introduction

- In the INBUILD trial in patients with chronic fibrosing ILDs with a progressive phenotype (other than idiopathic pulmonary fibrosis), nintedanib reduced the rate of decline in forced vital capacity (FVC) by 57% versus placebo.[1]
- The INBUILD trial population included patients with autoimmune disease-related ILDs, which are commonly treated using immunomodulatory therapies.

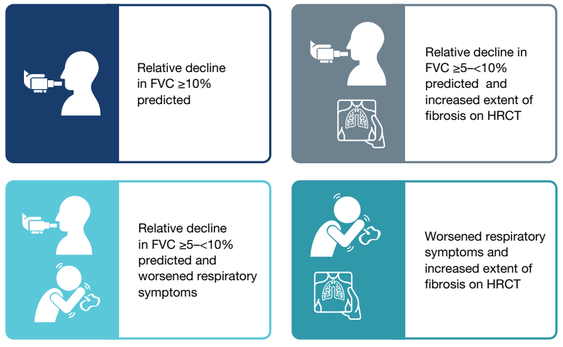
Aim

- To assess the potential effect of use of disease-modifying anti-rheumatic drugs (DMARDs) and/or glucocorticoids at baseline on the efficacy and safety of nintedanib in patients with progressive fibrosing autoimmune disease-related ILDs in the INBUILD trial.

Methods

Trial design[1]

- The INBUILD trial enrolled patients with an ILD other than idiopathic pulmonary fibrosis, diagnosed according to the investigator's usual clinical practice; ILD of >10% extent on a high-resolution computed tomography (HRCT) scan; FVC ≥45% predicted; diffusing capacity of the lungs for carbon monoxide ≥30%–<80% predicted.
- Patients met ≥1 of the following criteria for ILD progression in the 24 months before screening, despite management deemed appropriate in clinical practice:



- Patients taking stable doses of medications to treat autoimmune rheumatic diseases were eligible to participate, but the protocol excluded enrolment of patients treated with azathioprine, cyclosporine, mycophenolate, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids >20 mg/day. Investigators were asked not to consider patients with autoimmune disease that was managed using any of these restricted therapies for participation in the trial. Initiation of these therapies was allowed after 6 months of trial treatment in patients with deterioration of their ILD or autoimmune disease.
- Treatment with oral glucocorticoids at a dose of ≤20 mg/day prednisone or equivalent was permitted at randomisation and during the trial.

Analyses

- In patients with autoimmune disease-related ILDs, we assessed the rate of decline in FVC (mL/year) over 52 weeks in subgroups by use of DMARDs and/or glucocorticoids (any dose) at baseline (yes/no).
- DMARDs were based on WHO standardised drug groupings, including baricitinib and excluding denosumab. Glucocorticoids were based on WHO standardised drug groupings, restricted to oral, IV, or intramuscular administration.
- 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

Patients

- 170 patients in the INBUILD trial had autoimmune disease-related ILDs, of whom 131 were taking DMARDs and/or glucocorticoids at baseline.

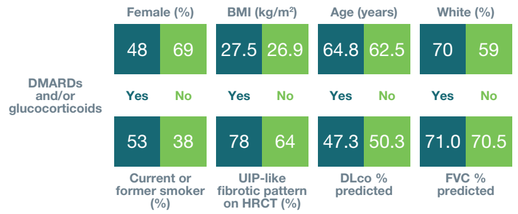
Among patients taking DMARDs and/or glucocorticoids at baseline (n=131):

Most frequently used therapies:

Prednisone	37.4%	Hydroxychloroquine /sulphate	19.8%	Abatacept	4.6%
Prednisolone	35.1%	Leflunomide	11.5%	Etanercept	3.1%
Methylprednisolone	8.4%	Methotrexate	11.5%	Tocilizumab	3.1%
Meprednisone	3.1%	Sulfasalazine	7.6%		

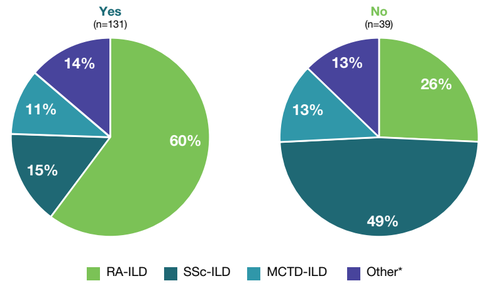
Therapies taken by ≥4 patients (3.1%) are shown.
All but 1 patient taking glucocorticoids at baseline took <20 mg/day.

Baseline characteristics of patients with autoimmune disease-related ILDs in subgroups by use of DMARDs and/or glucocorticoids



Mean or % of patients.
UIP, usual interstitial pneumonia

ILD diagnoses in patients with autoimmune disease-related ILDs in subgroups by use of DMARDs and/or glucocorticoids at baseline

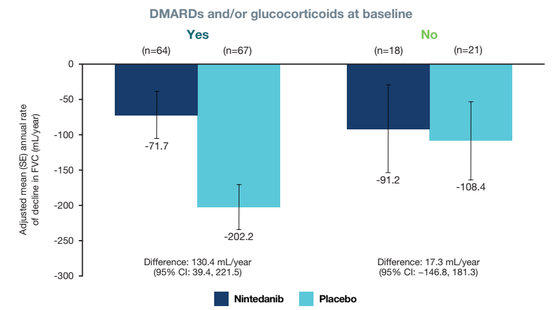


*Patients with an autoimmune disease noted in the "Other fibrosing ILDs" category of the case report form, including Sjogren's disease-related ILD, interstitial pneumonia with autoimmune features (IPAF), and undifferentiated autoimmune disease-related ILD.

Annual rate of decline in FVC (mL/year)

- In the placebo group, the rate of decline in FVC over 52 weeks was numerically greater in patients taking than not taking DMARDs and/or glucocorticoids at baseline (Figure 1).
- The effect of nintedanib versus placebo on reducing the rate of decline in FVC was numerically more pronounced in patients taking than not taking DMARDs and/or glucocorticoids at baseline, but the exploratory interaction p-value did not indicate heterogeneity in the treatment effect of nintedanib between the subgroups (Figure 1).

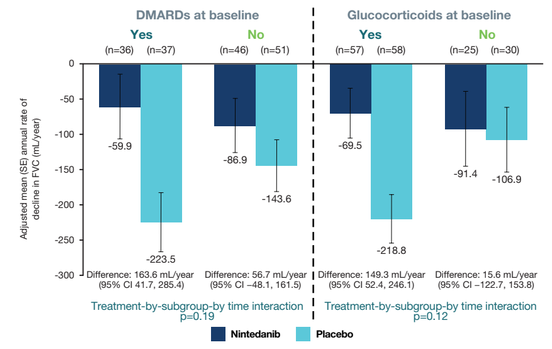
Figure 1. *Rate of decline in FVC (mL/year) over 52 weeks in patients with autoimmune disease-related ILDs in subgroups by use of DMARDs and/or glucocorticoids at baseline*



Treatment-by-time-by-subgroup interaction p=0.23

- Similar results were observed when subgroups by use of DMARDs and by use of glucocorticoids were analysed individually (Figure 2).

Figure 2. *Rate of decline in FVC (mL/year) over 52 weeks in patients with autoimmune disease-related ILDs in subgroups by use of DMARDs and by use of glucocorticoids at baseline*

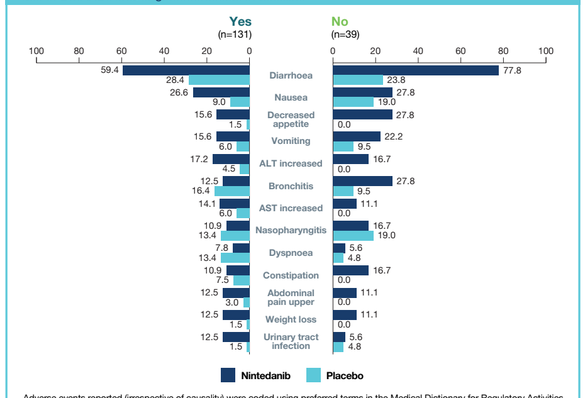


Treatment-by-subgroup-by time interaction p=0.19
Treatment-by-subgroup-by time interaction p=0.12

Adverse events

- The adverse event profile of nintedanib was similar in the subgroups by use of DMARDs and/or glucocorticoids at baseline (Figure 3).

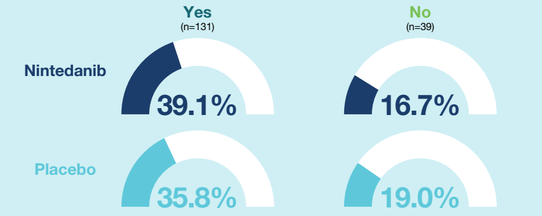
Figure 3. *Adverse events in patients with autoimmune disease-related ILDs in subgroups by use of DMARDs and/or glucocorticoids at baseline*



Adverse events reported (irrespective of causality) 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) in >10% of patients in either treatment group in the subgroup of patients with autoimmune disease-related ILDs.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- In both the nintedanib and placebo groups, serious adverse events were reported in a higher proportion of patients who were taking than not taking DMARDs and/or glucocorticoids at baseline (Figure 4).

Figure 4. *Proportions of patients with serious adverse events in subgroups by use of DMARDs and/or glucocorticoids at baseline*



Serious adverse events were defined as events that resulted in death, was life-threatening, resulted in hospitalisation or prolonged hospitalisation, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed serious for any other reason. Data are % of subjects with ≥1 such adverse event reported over 52 weeks.

Conclusions

- **In patients with chronic fibrosing autoimmune disease-related ILDs in the INBUILD trial, the rate of FVC decline in the placebo group was numerically greater in patients who were taking DMARDs and/or glucocorticoids at baseline than in those who were not.**
- **Both in patients who were and were not taking DMARDs and/or glucocorticoids at baseline, the rate of FVC decline was slower in patients treated with nintedanib than placebo; the interaction P-value did not indicate heterogeneity in the treatment effect of nintedanib between subgroups.**
- **Nintedanib had an acceptable safety profile both in patients who were and were not using DMARDs and/or glucocorticoids at baseline.**

References

1. Flaherty KR et al. N Engl J Med 2019;381:1718-1727.

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