Does HRCT pattern influence the effect of nintedanib in patients with progressive fibrosing interstitial lung diseases (ILDs)?

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Introduction

- Nintedanib has been approved by the FDA for the treatment of idiopathic pulmonary fibrosis (IPF), systemic sclerosis-associated ILD, and chronic fibrosing ILDs with a progressive phenotype.
- In the INBUILD trial conducted in subjects with chronic fibrosing ILDs with a progressive phenotype (other than IPF), nintedanib slowed the rate of decline in FVC versus placebo, with adverse events that were manageable for most subjects.[1]
- Previous studies suggested that the progression of progressive fibrosing ILDs is more rapid in subjects with a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT).[2,3]

Aim

- To assess the effect of nintedanib versus placebo in the INBUILD trial in subgroups by HRCT pattern.

Methods

Trial design

- Subjects had an ILD other than IPF, diagnosed according to the investigator's usual clinical practice; diffuse fibrosing interstitial lung disease 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:
  - Relative decline in FVC ≥10% predicted
  - Relative decline in FVC ≥5–<10% predicted and worsened respiratory symptoms
  - Relative decline in FVC ≥5–<10% predicted and increased extent of fibrosis on HRCT
  - Worsened respiratory symptoms and increased extent of fibrosis on HRCT.
- Subjects were randomized 1:1 to receive nintedanib 150 mg bid or placebo, stratified by HRCT pattern (UIP-like fibrotic pattern or other fibrotic patterns) based on central review by expert radiologists. There were two co-primary analysis populations: the overall population and subjects with a UIP-like fibrotic pattern on HRCT.

Fibrotic patterns on HRCT

A	Definite honeycomb lung destruction with basal and peripheral predominance
B	Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C	Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

A+B+C A+C B+C	UIP-like fibrotic pattern on HRCT
A+B A B None	Other fibrotic patterns on HRCT

Analyses

- In pre-specified analyses, we assessed the effect of nintedanib versus placebo on the following endpoints over 52 weeks in subgroups with a UIP-like fibrotic pattern and other fibrotic patterns on HRCT at baseline:
  - Rate of decline in FVC (mL/year)
  - Change from baseline in K-BILD questionnaire total score
  - Time to acute exacerbation or death
  - Time to absolute decline from baseline in FVC ≥10% predicted or death.
- 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.

Results

412 (62.1%) subjects had a UIP-like fibrotic pattern on HRCT

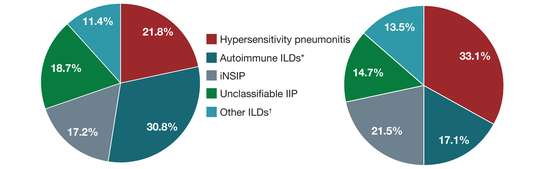
251 (37.9%) subjects had other fibrotic patterns on HRCT

Baseline characteristics of subgroups by fibrotic pattern on HRCT

	Male (%)		BMI (kg/m²)		Age (years)	
	UIP-like fibrotic pattern	Other fibrotic patterns	UIP-like fibrotic pattern	Other fibrotic patterns	UIP-like fibrotic pattern	Other fibrotic patterns
	60.0	43.4	27.6	29.4	68.0	62.1
	70.6	66.4	46.6	45.4	53.1	51.2
	FVC % predicted		DLco % predicted		K-BILD questionnaire total score	

Mean or % of subjects.

ILD diagnoses in subgroups by fibrotic pattern on HRCT

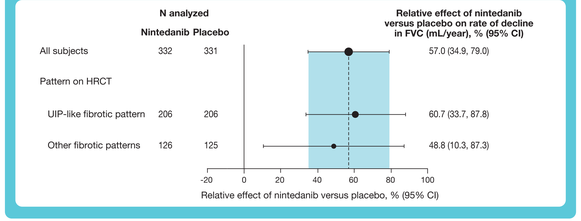


*Included ILD associated with rheumatoid arthritis, systemic sclerosis, and mixed connective tissue disease, plus subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of the case report form. †Included sarcoidosis, exposure-related ILDs and selected terms in the "Other fibrosing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

Annual rate of decline in FVC (mL/year)

- In subjects who received placebo, the rate of decline in FVC over 52 weeks was numerically greater in subjects with a UIP-like fibrotic pattern on HRCT than in those with other fibrotic patterns on HRCT (–209.2 [SE 19.1] versus –155.4 [23.6] mL/year).
- The difference between the nintedanib and placebo groups in the annual rate of decline in FVC was 127.8 (95% CI: 74.3, 181.2) mL/year in subjects with a UIP-like fibrotic pattern on HRCT and 75.4 (95% CI: 9.5, 141.4) mL/year in subjects with other fibrotic patterns on HRCT (treatment-by-subgroup-by-time interaction p=0.23).
- The relative treatment effect of nintedanib on the annual rate of decline in FVC was consistent between the subgroups by fibrotic pattern on HRCT:

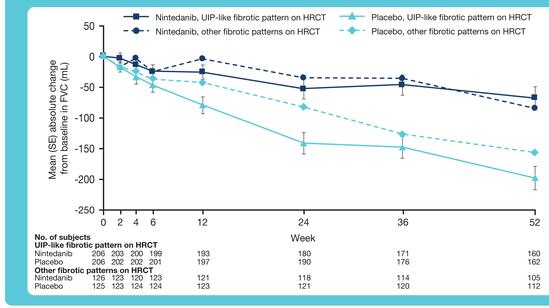
Relative effect of nintedanib versus placebo on the annual rate of decline in FVC (mL/year) over 52 weeks in subgroups by fibrotic pattern on HRCT



Observed change in FVC over 52 weeks

- The observed change from baseline over time showed clear separation between the nintedanib and placebo groups, both in subjects with a UIP-like fibrotic pattern on HRCT and in subjects with other fibrotic patterns on HRCT:

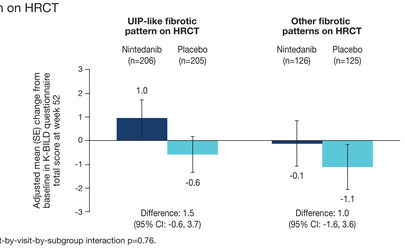
Observed change from baseline in FVC (mL) over 52 weeks in subgroups by fibrotic pattern on HRCT



Change in K-BILD questionnaire total score at week 52

- There was no meaningful change in total score on the K-BILD questionnaire with nintedanib versus placebo in either subgroup by fibrotic pattern on HRCT:

Change from baseline in K-BILD questionnaire total score at week 52 in subgroups by fibrotic pattern on HRCT



Treatment-by-visit-by-subgroup interaction p=0.76.
K-BILD questionnaire total scores range from 0–100, with higher scores representing better health status.

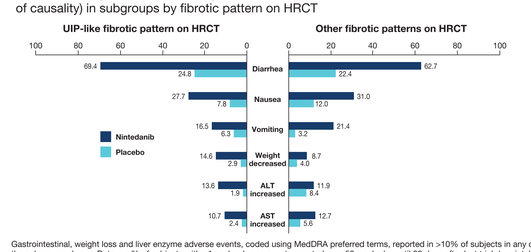
Time to first acute exacerbation of ILD or death, and absolute decline in FVC ≥10% predicted or death

	UIP-like fibrotic pattern on HRCT		Other fibrotic patterns on HRCT	
	Nintedanib (n=206)	Placebo (n=206)	Nintedanib (n=126)	Placebo (n=125)
Acute exacerbation of ILD or death over 52 weeks, n (%)	17 (8.3)	25 (12.1)	9 (7.1)	7 (5.6)
HR (95% CI)	0.67 (0.36, 1.24)		1.26 (0.47, 3.39)	
Treatment-by-subgroup interaction	p=0.28			
Absolute decline in FVC ≥10% predicted or death over 52 weeks, n (%)	56 (27.2)	82 (39.8)	29 (23.0)	42 (33.6)
HR (95% CI)	0.64 (0.45, 0.89)		0.67 (0.42, 1.07)	
Treatment-by-subgroup interaction	p=0.84			

Adverse events

- In both subgroups by HRCT pattern, the adverse event profile of nintedanib was consistent with the overall population:

Most frequent gastrointestinal, weight loss and hepatic adverse events (reported irrespective of causality) in subgroups by fibrotic pattern on HRCT



Gastrointestinal, weight loss and liver enzyme adverse events, coded using MedDRA preferred terms, reported in >10% of subjects in any of the subgroups shown. 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). ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- Serious adverse events occurred in 30.6% and 34.9% of subjects treated with nintedanib, compared with 37.4% and 26.4% of subjects who received placebo, in the subgroups with a UIP-like fibrotic pattern on HRCT and other fibrotic patterns on HRCT, respectively.
- Fatal adverse events occurred in 3.4% and 3.2% of subjects treated with nintedanib, compared with 7.8% and 0.8% of subjects who received placebo, in the subgroups with a UIP-like fibrotic pattern on HRCT and other fibrotic patterns on HRCT, respectively.

Conclusions

- **In subjects with chronic fibrosing ILDs and a progressive phenotype who received placebo in the INBUILD trial, the annual rate of decline in FVC was numerically greater in subjects with a UIP-like fibrotic pattern on HRCT than in those with other fibrotic patterns on HRCT.**
- **The relative treatment effect of nintedanib on slowing the rate of FVC decline was consistent between subjects with a UIP-like fibrotic pattern and other fibrotic patterns on HRCT and similar to that observed in subjects with IPF in the INPULSIS trials.[4]**
- **Nintedanib was associated with a numerically reduced risk of an absolute decline in FVC ≥10% predicted or death in both subgroups by fibrotic pattern on HRCT.**

References

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Acknowledgements

The INBUILD trial was funded by Boehringer Ingelheim. Editorial and formatting assistance, supported financially by Boehringer Ingelheim, was provided by Elizabeth Ng and Wendy Morris of FleishmanHillard Fishburn, London, UK during preparation of this poster. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. Boehringer Ingelheim was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations. The authors received no direct compensation related to the development of this poster. Kevin Brown reports grants from NHLBI; personal fees from Biogen, Blade Therapeutics, Galapagos, Galecto Biotech, Huitai Biomedicine, Lifemax, Lilly, MedImmune, monARC Bionetworks, Pliant Therapeutics, ProMetic, Third Pole Therapeutics, Theravance, Three Lakes Partners, and Veracyte; personal fees and non-financial support from Boehringer Ingelheim; and other support from Genoa and the Open Source Imaging Consortium (OSIC). Athol Wells reports personal fees from Blade Therapeutics, Boehringer Ingelheim, and InterMune/Roche.

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Poster developed for the American Thoracic Society International Conference, 2020.