Relationship between body mass index (BMI) and decline in FVC in patients with IPF

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Introduction

- Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease characterised by loss of lung function.[1]
- There is some evidence that lower body mass index (BMI) is associated with a worse prognosis in patients with IPF, although this has not been observed in all studies.[2–5]
- In the two 52-week INPULSIS trials, nintedanib reduced the rate of decline in FVC (mL/year) in patients with IPF by approximately 50%, with an adverse event profile characterised mainly by gastrointestinal events.[6]

Aim

- To assess whether BMI at baseline was associated with disease progression or influenced the treatment effect of nintedanib in the INPULSIS trials.

Methods

Study design

- In the INPULSIS trials, patients with IPF with FVC ≥50% predicted and DLco 30–79% predicted were randomised 3:2 to receive nintedanib 150 mg bid or placebo for 52 weeks. The primary endpoint was the annual rate of decline in FVC (mL/year).[6]

Analyses

- Analyses were conducted *post-hoc* using pooled data from patients who received ≥1 dose of trial drug.
- We assessed the following outcomes over 52 weeks in subgroups by BMI below and at least the median at baseline:
  - Annual rate of decline in FVC (mL/year)
  - Absolute changes from baseline in FVC (mL and % predicted)
  - Absolute change from baseline in St George's Respiratory Questionnaire (SGRQ) total score
  - Time to absolute decline in FVC ≥10% predicted or death
  - Time to first investigator-reported acute exacerbation
  - Time to death
- The annual rate of decline in FVC was analysed using a random coefficient regression model (with random slopes and intercepts) with fixed effects for trial, treatment, gender, age, and height and treatment-by-subgroup, time-by-subgroup and treatment-by-time-by-subgroup interactions.
- Absolute changes in FVC and SGRQ total score were analysed using a mixed model for repeated measures.
- Time to event analyses were based on Cox regression.
- Interaction p-values were calculated to assess potential heterogeneity in the effect of nintedanib versus placebo between the subgroups, with no adjustment for multiple testing.
- Adverse events are presented descriptively.

Results

Patients

- 1061 patients were treated (638 with nintedanib and 423 with placebo).
- Median BMI at baseline was 27 kg/m².
- Compared with patients with BMI ≥27 kg/m², greater proportions of patients with BMI <27 kg/m² were of Asian race, had never smoked, and had emphysema. Mean (SD) FVC % predicted in patients with BMI <27 kg/m² and ≥27 kg/m² was 81.3 (18.4) and 78.1 (17.2), respectively (Table 1).
- The planned observation time was completed by 80.0% and 86.3% of patients with BMI <27 kg/m² and ≥27 kg/m², respectively.

***Table 1**. Baseline characteristics in subgroups of patients by BMI below and at least the median (27 kg/m²).*

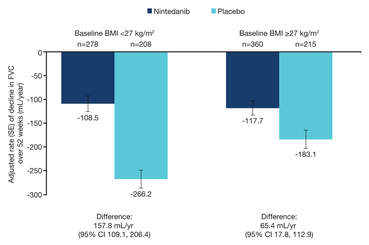
	Baseline BMI <27 kg/m²		Baseline BMI ≥27 kg/m²	
	Nintedanib (n=278)	Placebo (n=208)	Nintedanib (n=360)	Placebo (n=215)
Age, years, mean (SD)	67.7 (8.6)	67.2 (8.4)	65.8 (7.7)	66.7 (7.4)
Male, n (%)	219 (78.8)	163 (78.4)	288 (80.0)	171 (79.5)
Weight, kg, mean (SD)	66.8 (9.9)	67.3 (9.9)	88.9 (14.1)	89.6 (14.1)
Body mass index, kg/m², mean (SD)	24.1 (2.1)	24.0 (2.0)	31.1 (3.5)	31.1 (3.5)
Race, n (%)				
White	93 (33.5)	89 (42.8)	267 (74.2)	159 (74.0)
Asian	146 (52.5)	103 (49.5)	48 (13.3)	25 (11.6)
Black	1 (0.4)	0	1 (0.3)	0
Missing*	38 (13.7)	16 (7.7)	44 (12.2)	31 (14.4)
Time since diagnosis of IPF, years, mean (SD)	1.6 (1.4)	1.5 (1.3)	1.7 (1.3)	1.7 (1.3)
Current or former smoker, n (%)	199 (71.6)	138 (66.3)	265 (73.6)	163 (75.8)
FVC, mL, mean (SD)	2696 (753)	2697 (808)	2727 (761)	2758 (813)
FVC, % predicted, mean (SD)	82.2 (18.0)	80.1 (19.0)	77.9 (17.0)	78.5 (17.4)
SpO_2†, %, mean (SD)	96.1 (2.1)	96.1 (2.1)	95.7 (2.4)	95.5 (2.0)
DLco†, % predicted, mean (SD)	45.9 (13.5)	45.6 (14.1)	48.6 (13.4)	48.3 (12.6)
SGRQ total score, mean (SD)	36.7 (19.6)	38.2 (19.3)	41.7 (18.6)	40.9 (17.7)
Emphysema‡, n (%)	129 (46.4)	87 (41.8)	125 (34.7)	79 (36.7)

*In France, regulation did not permit the collection of data on race.
†Corrected for haemoglobin.
‡Based on qualitative assessment of HRCT scans by the investigator. Emphysema was classified as present or absent.

Annual rate of decline in FVC

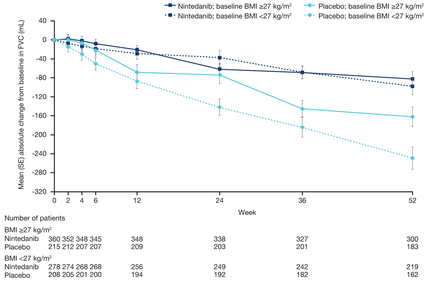
- In the placebo group, the mean rate of decline in FVC over 52 weeks was numerically greater in patients with baseline BMI <27 kg/m² than ≥27 kg/m² (Figures 1 and 2).
- Nintedanib reduced the rate of decline in FVC over 52 weeks both in patients with BMI <27 kg/m² and ≥27 kg/m², with a greater treatment effect in patients with BMI <27 kg/m² (p=0.0074 for treatment-by-time-by-subgroup interaction) (Figures 1 and 2).

***Figure 1**. Annual rate of decline in FVC (mL/year) assessed over 52 weeks by baseline BMI below and at least the median (27 kg/m²).*



P-value for treatment-by-time-by-subgroup interaction = 0.0074

***Figure 2.** Change from baseline in FVC (mL) over 52 weeks by baseline BMI below and at least the median (27 kg/m²).*



Other outcomes

- In the placebo group, the mean increase (worsening) in SGRQ total score at week 52, proportion of patients who had an acute exacerbation, and proportion of patients who died were numerically greater in patients with baseline BMI <27 kg/m² than ≥27 kg/m² (Table 2).
- Differences between the nintedanib and placebo groups in these outcomes were numerically greater in patients with BMI <27 kg/m² than ≥27 kg/m², but p-values did not indicate heterogenous treatment effects between the subgroups (Table 2).

***Table 2**. Outcomes in subgroups of patients by baseline BMI below and at least the median (27 kg/m²).*

	Baseline BMI <27 kg/m²		Baseline BMI ≥27 kg/m²	
	Nintedanib (n=278)	Placebo (n=208)	Nintedanib (n=360)	Placebo (n=215)
Absolute change from baseline in FVC (mL) over 52 weeks, adjusted mean (SE)	-114.8 (18.4)	-264.3 (21.2)	-101.2 (15.4)	-167.3 (19.8)
Difference versus placebo (95% CI)	149.5 (94.4, 204.5)		66.0 (16.8, 115.2)	
Treatment-by-subgroup interaction	p=0.64			
Absolute change from baseline in FVC % predicted over 52 weeks, adjusted mean (SE)	-3.7 (0.6)	-8.0 (0.6)	-3.0 (0.4)	-4.8 (0.6)
Difference versus placebo (95% CI)	4.3 (2.6, 6.0)		1.8 (0.4, 3.2)	
Treatment-by-subgroup interaction	p=0.37			
Acute exacerbation of IPF over 52 weeks, n (%)	17 (6.1)	19 (9.1)	14 (3.9)	13 (6.0)
HR (95% CI)	0.65 (0.34, 1.26)		0.65 (0.31, 1.40)	
p-value for treatment-by-subgroup interaction	p=0.96			
Absolute change from baseline in SGRQ total score over 52 weeks, adjusted mean (SE)	4.1 (1.0)	6.7 (1.2)	3.5 (0.9)	3.9 (1.1)
Difference versus placebo (95% CI)	-2.6 (-5.7, 0.6)		-0.4 (-3.2, 2.3)	
Treatment-by-subgroup interaction	p=0.80			
Absolute decline in FVC ≥10% predicted or death at week 52, n (%)	74 (26.6)	94 (45.2)	99 (27.5)	81 (37.7)
HR (95% CI)	0.49 (0.36, 0.67)		0.71 (0.53, 0.95)	
Treatment-by-subgroup interaction	p=0.14			
Deaths, n (%)	14 (5.0)	21 (10.1)	21 (5.8)	12 (5.6)
HR (95% CI)	0.46 (0.24, 0.92)		1.07 (0.53, 2.19)	
Treatment-by-subgroup interaction	p=0.11			

HR, hazard ratio.

Adverse events

- In the nintedanib and placebo groups, greater proportions of patients with baseline BMI <27 kg/m² than ≥27 kg/m² had adverse events of decreased appetite, weight decrease, and progression of IPF, and smaller proportions had bronchitis (Table 3).
- The adverse event profile of nintedanib was similar between the subgroups (Table 3).

***Table 3.** Adverse events in subgroups of patients by baseline BMI below and at least the median (27 kg/m²).*

	Baseline BMI <27 kg/m²		Baseline BMI ≥27 kg/m²	
	Nintedanib (n=278)	Placebo (n=208)	Nintedanib (n=360)	Placebo (n=215)
Adverse event(s)	263 (94.6)	183 (88.0)	346 (96.1)	196 (91.2)
Most frequent adverse event(s)*				
Diarrhoea	163 (58.6)	37 (17.8)	230 (63.9)	41 (19.1)
Nausea	68 (24.5)	12 (5.8)	88 (24.4)	16 (7.4)
Progression of IPF†	33 (11.9)	42 (20.2)	31 (8.6)	19 (8.8)
Nasopharyngitis	49 (17.6)	35 (16.8)	38 (10.6)	33 (15.3)
Cough	29 (10.4)	29 (13.9)	56 (15.6)	28 (13.0)
Decreased appetite	37 (13.3)	20 (9.6)	31 (8.6)	4 (1.9)
Bronchitis	21 (7.6)	15 (7.2)	46 (12.8)	30 (14.0)
Dyspnoea	16 (5.8)	21 (10.1)	33 (9.2)	27 (12.6)
Vomiting	33 (11.9)	7 (3.4)	41 (11.4)	4 (1.9)
Upper respiratory tract infection	27 (9.7)	18 (8.7)	31 (8.6)	24 (11.2)
Weight decreased	31 (11.2)	10 (4.8)	31 (8.6)	5 (2.3)
Adverse event(s) leading to treatment discontinuation	67 (24.1)	29 (13.9)	56 (15.6)	26 (12.1)
Severe adverse event(s)‡	74 (26.6)	52 (25.0)	100 (27.8)	47 (21.9)
Serious adverse event(s)§	91 (32.7)	62 (29.8)	103 (28.6)	65 (30.2)
Fatal adverse event(s)	13 (4.7)	17 (8.2)	24 (6.7)	14 (6.5)

Data are n (%) of patients with ≥1 such adverse event reported over 52 weeks plus a 4-week post-treatment follow-up period.
*Adverse events by MedDRA preferred term reported in ≥10% of patients in ≥1 of the subgroups shown.
†Corresponds to MedDRA term 'IPF', which included disease worsening and acute exacerbations.
‡Event that was incapacitating or that caused an inability to work or to perform usual activities.
§Event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalisation, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.

Conclusions

- **Post-hoc analyses of data from the INPULSIS trials suggest that the rate of decline in FVC over 52 weeks was greater in untreated patients with BMI below than above the median at baseline.**
- **Nintedanib reduced the annual rate of decline in FVC both in patients with baseline BMI below and above the median, with a greater treatment effect in patients with lower BMI. The decline in FVC in patients treated with nintedanib was similar in patients with baseline BMI below and above the median.**
- **The adverse event profile of nintedanib was similar between patients with baseline BMI below and above the median.**

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