Effect of dose reductions and/or interruptions on the efficacy of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): subgroup analysis of the INPULSIS® trials

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Introduction

- Nintedanib is approved for the treatment of idiopathic pulmonary fibrosis (IPF) in several countries and regions, including the US, Europe and Japan.
- The efficacy and safety of nintedanib 150 mg twice daily (bid) were assessed in the two replicate Phase III, placebo-controlled, 52-week INPULSIS® trials. In both trials, nintedanib significantly reduced disease progression by reducing the annual rate of decline in forced vital capacity (FVC).[1]
- Dose reductions from 150 mg bid to 100 mg bid and treatment interruptions were recommended for the management of adverse events. Following a dose reduction, the dose could be escalated back to 150 mg bid; following treatment interruption, nintedanib could be restarted at a dose of 150 mg bid or 100 mg bid.

Aim

- To assess whether dose reductions and/or treatment interruptions influenced the effect of nintedanib on reducing FVC decline.

Methods

- Data from both INPULSIS® trials were pooled.
- Annual rate of decline in FVC (mL/year) in patients treated with nintedanib and placebo were assessed in the following subgroups:
  - Patients who had no dose reduction or treatment interruption
  - Patients who took 150 mg bid as their last dose and had ≥1 dose reduction and/or treatment interruption
  - Patients who took 100 mg bid as their last dose after ≥1 dose reduction and/or treatment interruption
  - Patients with a dose intensity of <80% versus ≥80%.
- Dose intensity was defined as the amount of drug administered over the study divided by the amount of drug that would have been received had the 150 mg bid dose been administered throughout the 52-week treatment period or until permanent treatment discontinuation.
- To assess the consistency of the treatment effect of nintedanib on the annual rate of decline in FVC across subgroups, treatment-by-time-by-subgroup interaction p-values were calculated.
- Analyses were based on patients who received ≥1 dose of study drug.

Results

- A total of 1061 patients were included in the analyses (638 treated with nintedanib, 423 with placebo).
- Most (75%) patients did not have any dose reductions or treatment interruptions.
- Baseline characteristics were generally similar between subgroups defined by dose reduction and/or treatment interruption (Table 1) and by dose intensity (Table 2), although patients who took 100 mg bid as their last dose tended to be older.

Table 1. *Baseline characteristics of subgroups by dose reduction and/or treatment interruption*

	No dose reduction or treatment interruption		150 mg bid as last dose and ≥1 dose reduction and/or treatment interruption		100 mg bid as last dose after ≥1 dose reduction and/or treatment interruption	
	Nintedanib (n=418)	Placebo (n=377)	Nintedanib (n=69)	Placebo (n=37)	Nintedanib (n=151)	Placebo (n=9)
Age, years, mean (SD)	65.9 (7.9)	66.6 (7.9)	67.4 (8.2)	69.6 (6.8)	68.2 (8.4)	72.1 (8.9)
Male, n (%)	352 (84)	295 (78)	58 (84)	32 (86)	97 (64)	7 (78)
Race, n (%)						
White	225 (54)	220 (58)	44 (64)	22 (60)	91 (60)	6 (67)
Asian	137 (33)	115 (31)	17 (25)	10 (27)	40 (26)	3 (33)
Black	1 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Missing*	55 (13)	42 (11)	7 (10)	5 (14)	20 (13)	0 (0)
Former or current smoker, n (%)	308 (74)	267 (71)	57 (83)	25 (68)	99 (66)	9 (100)
FVC, mL, mean (SD)	2787 (757)	2734 (813)	2733 (776)	2751 (855)	2501 (713)	2355 (384)
FVC, % predicted, mean (SD)	79.1 (17.2)	79.6 (18.1)	81.2 (17.5)	78.3 (21.4)	80.9 (18.6)	71.3 (8.2)
DLco, mmol/min/kPa, mean (SD)	4.0 (1.3)	3.9 (1.3)	3.7 (1.0)	3.6 (0.9)	3.7 (1.2)	3.1 (0.7)
FEV_1/FVC ratio, %, mean (SD)	81.5 (5.6)	81.6 (6.0)	81.9 (6.9)	81.7 (6.0)	81.9 (5.9)	82.6 (5.6)

*In France, regulation did not permit the collection of data on race.

Table 2. *Baseline characteristics of subgroups by dose intensity*

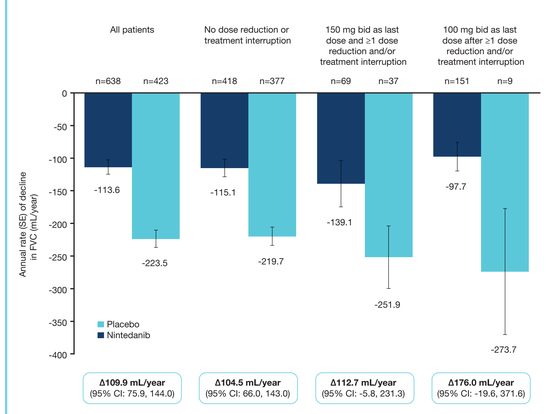
	Dose intensity <80%		Dose intensity ≥80%	
	Nintedanib (n=92)	Placebo (n=6)	Nintedanib (n=546)	Placebo (n=417)
Age, years, mean (SD)	68.2 (8.8)	73.3 (10.3)	66.3 (8.0)	66.9 (7.8)
Male, n (%)	53 (58)	4 (67)	454 (83)	330 (79)
Race, n (%)				
White	61 (66)	5 (83)	299 (55)	243 (58)
Asian	25 (27)	1 (17)	169 (31)	127 (30)
Black	0 (0)	0 (0)	2 (0)	0 (0)
Missing*	6 (7)	0 (0)	76 (14)	47 (11)
Former or current smoker, n (%)	66 (72)	5 (83)	398 (73)	296 (71)
FVC, mL, mean (SD)	2414 (634)	2386 (368)	2764 (765)	2733 (814)
FVC, % predicted, mean (SD)	81.3 (19.2)	78.5 (16.4)	79.5 (17.3)	79.3 (18.3)
DLco, mmol/min/kPa, mean (SD)	3.7 (1.2)	3.2 (0.7)	3.9 (1.2)	3.9 (1.2)
FEV_1/FVC ratio, %, mean (SD)	82.6 (6.2)	82.6 (4.3)	81.5 (5.8)	81.7 (6.0)

*In France, regulation did not permit the collection of data on race.
Dose intensity was defined as the amount of drug administered over the study divided by the amount of drug that would have been received had the 150 mg bid dose been administered throughout the 52-week treatment period or until permanent treatment discontinuation.

Dose reductions and/or treatment interruptions

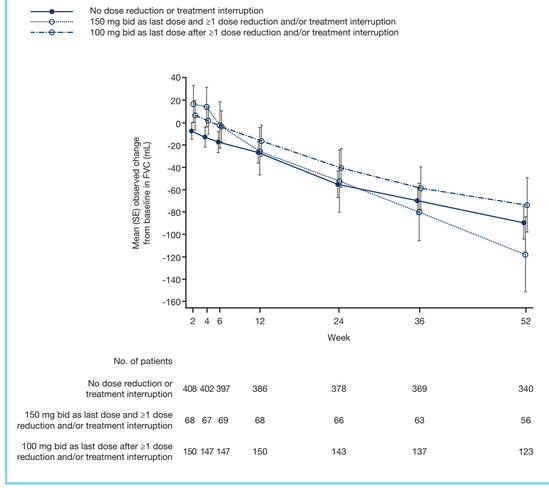
- In patients who took nintedanib 150 mg bid as their last dose, the adjusted annual rates of decline in FVC were –139.1 mL/year in patients who had ≥1 dose reduction and/or treatment interruption and –115.1 mL/year in patients who did not have any dose reductions or treatment interruptions.
- In patients who took nintedanib 100 mg bid as their last dose, the adjusted annual rate of decline in FVC was –97.7 mL/year.
- The treatment effect of nintedanib was consistent across the three subgroups by dose reduction and/or treatment interruption (p=0.7765).
- In patients treated with nintedanib, the annual rates of decline in FVC in every subgroup were similar to the annual rate of decline in FVC in the overall patient population (Figure 1).

Figure 1. *Annual rate of decline in FVC in patients by last dose and whether they had ≥1 dose reduction and/or treatment interruption*



- Changes from baseline in FVC over time were similar in patients treated with nintedanib irrespective of dose reductions and/or treatment interruptions (Figure 2).

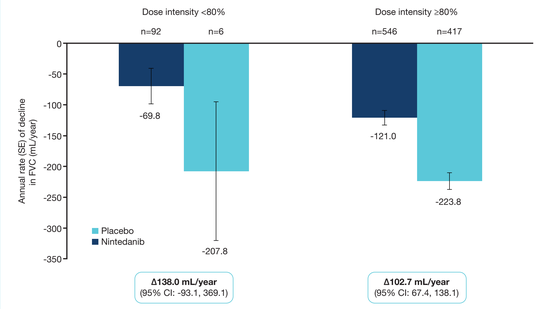
Figure 2. *Change from baseline in FVC over time in patients treated with nintedanib by last dose and whether they had a dose reduction and/or treatment interruption*



Dose intensity

- Ninety-two patients (14.4%) in the nintedanib group had a dose intensity of <80%, compared with 6 patients (1.4%) in the placebo group.
- The treatment effect of nintedanib was not significantly different between the subgroups by dose intensity (p=0.8102) (Figure 3).

Figure 3. *Annual rate of decline in FVC by dose intensity*



Conclusions

- **Pooled data from the INPULSIS® trials showed that disease progression, as measured by the rate of decline in FVC, was similar in patients treated with nintedanib irrespective of whether they had temporary or permanent dose reductions and/or treatment interruptions.**
- **These results suggest that the dosing regimen used in the INPULSIS® trials, which allowed for dose reductions and treatment interruptions to manage adverse events, was effective at reducing disease progression in patients with IPF. These data should not be interpreted as suggesting that 100 mg bid should be the starting dose of nintedanib in patients with IPF.**

Reference

1. Richeldi L et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071–82.

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