Therapeutic effects of nintedanib are not influenced by emphysema in the INPULSIS trials

To the Editor:

Emphysema is a common comorbidity in patients with idiopathic pulmonary fibrosis (IPF) [1–4]. Due to the combination of restrictive and obstructive effects, patients with concomitant IPF and emphysema typically present with normal or elevated forced vital capacity (FVC) but reduced diffusing capacity [5]. Data from retrospective studies have demonstrated that lung function decline is attenuated in patients with IPF who have emphysema [6], with some evidence suggesting a threshold for extent of emphysema beyond which FVC decline is reduced [7].

Nintedanib is a tyrosine kinase inhibitor approved for the treatment of IPF. In the two Phase III INPULSIS trials, nintedanib reduced disease progression by reducing the annual rate of decline in FVC (the primary end-point) *versus* placebo (difference of 109.9 mL·year^{-1}, 95% CI 75.9–144.0, based on pooled data) [8]. Based on pooled data, nintedanib was associated with numerical but not statistically significant benefits on the key secondary end-points of time to first investigator-reported acute exacerbation and change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 52 weeks [8]. To participate in the INPULSIS trials, patients were required to have an FVC ⩾50% predicted, a forced expiratory volume in 1 s (FEV_1)/FVC ratio of ⩾0.7 and a diffusing capacity of the lungs for carbon monoxide (D_{LCO}) 30–79% predicted. The presence of emphysema (yes/no) at screening was determined by qualitative assessment of high-resolution computed tomography (HRCT) scans by a single expert radiologist.

We investigated whether the presence of emphysema, or the degree of airway obstruction assessed by FEV_1/FVC ratio, at baseline influenced the treatment effect of nintedanib in the INPULSIS trials. In *post hoc* analyses, the primary analyses of the primary and key secondary end-points (described in [8]) were repeated in subgroups of patients with *versus* without emphysema at baseline and with a baseline FEV_1/FVC ratio ⩾0.7 and ⩽0.8 *versus* >0.8 (a threshold chosen arbitrarily). For the primary end-point, the term subgroup and the interaction terms treatment-by-subgroup, time-by-subgroup and treatment-by-time-by-subgroup were included in the model. For the key secondary end-points, the term subgroup and interaction term treatment-by-subgroup were included in the model. Absolute change from baseline in composite physiologic index (CPI) over 52 weeks was also assessed in these subgroups. The CPI is calculated based on per cent predicted values for FVC, D_{LCO} and FEV_1 and correlates with extent of fibrosis on HRCT, irrespective of the presence of emphysema [9].

Of the 1061 patients treated in the INPULSIS trials, 420 (39.6%) had emphysema based on qualitative assessment of an HRCT scan (yes/no) and 412 (38.8%) had a baseline FEV_1/FVC ratio ⩽0.8 at baseline. Baseline characteristics were generally similar between the subgroups by emphysema at baseline and by FEV_1/FVC ratio ⩽0.8 *versus* >0.8 at baseline, except for a higher proportion of males and ex-/current smokers in the subgroups with emphysema and with an FEV_1/FVC ratio ⩽0.8. The effect of nintedanib on FVC decline was consistent between patients with or without emphysema at baseline. In patients with emphysema at baseline, the adjusted annual rate±SE of decline in FVC was −105.1±18.8 mL·year^{-1} with nintedanib and −207.2±23.2 mL·year^{-1} with placebo (difference of 102.0 mL·year^{-1}, 95% CI 43.2–160.9) while in patients without emphysema, it was −118.8±13.4 mL·year^{-1} with nintedanib and −234.2±16.4 mL·year^{-1}

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In *post hoc* analyses of pooled data from the INPULSIS trials, the treatment effect of nintedanib *versus* placebo was not influenced by the presence of emphysema (yes *versus* no) or by FEV_1/FVC ratio (⩾0.7 to ⩽0.8 *versus* >0.8) at baseline http://ow.ly/Gmwn30nwPY1

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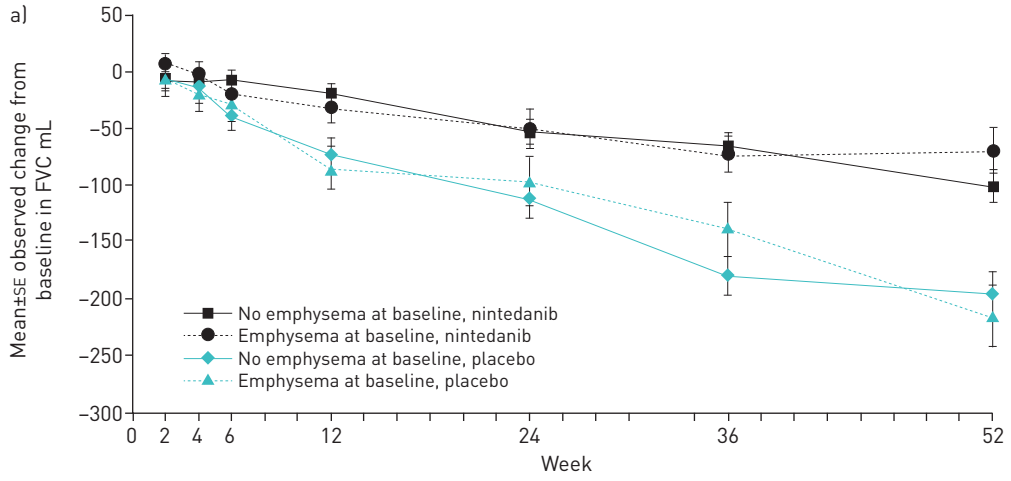
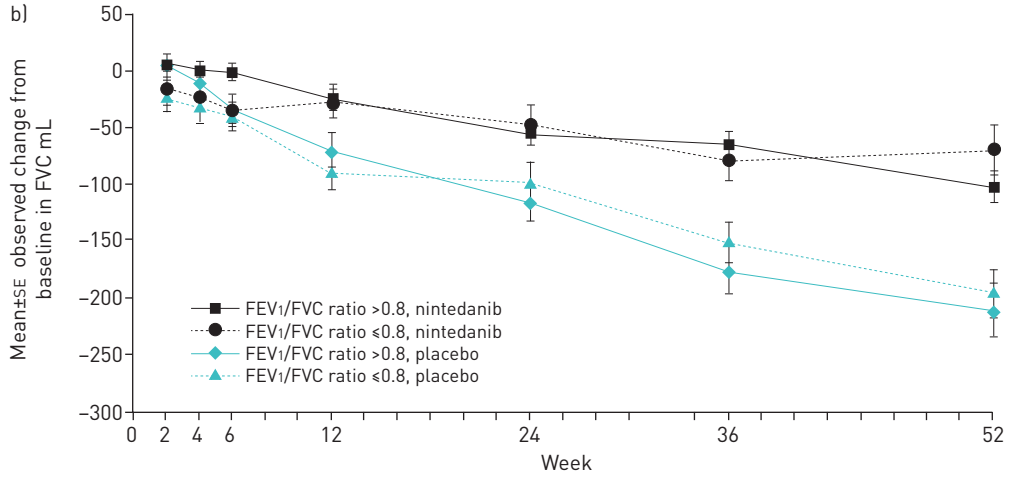


Patients n							
No emphysema at baseline, nintedanib	379	375	372	366	359	349	316
Emphysema at baseline, nintedanib	247	241	241	238	228	220	203
No emphysema at baseline, placebo	252	248	245	246	244	236	212
Emphysema at baseline, placebo	165	160	162	157	151	147	133



Patients n							
FEV_1/FVC ratio >0.8, nintedanib	394	389	387	383	373	363	328
FEV_1/FVC ratio ≤0.8, nintedanib	232	227	226	221	214	206	191
FEV_1/FVC ratio >0.8, placebo	245	237	237	233	227	216	191
FEV_1/FVC ratio ≤0.8, placebo	172	171	170	170	168	167	154

FIGURE 1: Mean±SE observed change from baseline in forced vital capacity (FVC) over time in subgroups of patients by a) presence of emphysema at baseline and b) forced expiratory volume in 1 s (FEV_1)/FVC ratio at baseline.

with placebo (difference of 115.4 mL·year^{-1}, 95% CI 73.8–157.1) (treatment-by-time-by-subgroup interaction p=0.6771). The effect of nintedanib on FVC decline was consistent between patients with a baseline FEV_1/FVC ratio ⩽0.8 *versus* >0.8. In patients with an FEV_1/FVC ratio ⩽0.8, the adjusted annual rate±SE of decline in FVC was −88.6±18.1 mL·year^{-1} with nintedanib and −184.0±20.3 mL·year^{-1} with placebo (difference of 95.5 mL·year^{-1}, 95% CI 41.9–149.1) while in patients with an FEV_1/FVC ratio >0.8, it was −128.1±13.8 mL·year^{-1} with nintedanib and −254.2±17.9 mL·year^{-1} with placebo (difference of 126.1 mL·year^{-1}, 95% CI 81.6–170.6) (treatment-by-time-by-subgroup interaction p=0.3735). Consistent results were observed for changes from baseline in FVC over time (figure 1). In patients with emphysema at baseline, the adjusted mean±SE change from baseline in CPI was 3.5±0.7 with nintedanib and 3.4±0.8 with placebo (difference of 0.2, 95% CI −1.5–1.9); while in patients without emphysema, it was 2.5±0.6 with nintedanib and 4.3±0.7 with placebo (difference of −1.9, 95% CI −3.5–−0.3) (treatment-by-subgroup interaction p=0.2328). In patients with an FEV_1/FVC ratio ⩽0.8, the adjusted mean±SE change from baseline in CPI was 3.0±0.8 with nintedanib and 3.6±0.8 with placebo (difference of −0.7, 95% CI −2.4–1.1); while in patients with an FEV_1/FVC ratio >0.8, it was 2.7±0.5 with nintedanib and 4.4±0.7 with placebo (difference of −1.6, 95% CI −3.2–0.0) (treatment-by-subgroup interaction p=0.8797).

In patients with emphysema at baseline, acute exacerbations occurred in 2.8% and 7.2% of patients treated with nintedanib and placebo, respectively. In patients without emphysema at baseline, acute exacerbations occurred in 6.3% and 7.8% of patients treated with nintedanib and placebo, respectively. The hazard ratio for time to first acute exacerbation was 0.36 (95% CI 0.14–0.91) in patients with emphysema and 0.82 (95% CI 0.45–1.49) in patients without emphysema at baseline, but the treatment-by-subgroup interaction was not significant (p=0.1449). The effect of nintedanib on reducing the risk of a first acute exacerbation was not significantly different between patients with a baseline FEV1/FVC ratio ⩽0.8 *versus* >0.8 (treatment-by-subgroup interaction p=0.6118). The hazard ratio for time to first acute exacerbation was 0.79 (95% CI 0.28–2.25) in patients with an FEV1/FVC ratio ⩽0.8 and 0.57 (95% CI 0.33–1.00) in patients with an FEV1/FVC ratio >0.8. Acute exacerbations occurred in 3.0% and 4.0% of nintedanib- and placebo-treated patients with an FEV1/FVC ratio ⩽0.8, and 6.0% and 10.1% of nintedanib- and placebo-treated patients with an FEV1/FVC ratio >0.8.

The effect of nintedanib on change in SGRQ total score was consistent between patients with or without emphysema. Nintedanib- and placebo-treated patients with a baseline FEV1/FVC ratio >0.8 had a numerically greater increase (worsening) in SGRQ total score (4.43 and 7.27 points, respectively) than nintedanib- and placebo-treated patients with a baseline FEV1/FVC ratio ⩽0.8 (1.95 and 2.16 points, respectively). Between-group differences in change from baseline in SGRQ total score were −1.71 points (95% CI −4.32–0.90) in patients with emphysema and −1.23 points (95% CI −3.39–0.92) in patients without emphysema (treatment-by-subgroup interaction p=0.7723). Between-group differences in change from baseline in SGRQ total score were −0.21 points (95% CI −2.71–2.29) in patients with a baseline FEV1/FVC ratio ⩽0.8 and −2.83 points (95% CI −5.04–−0.63) in patients with a baseline FEV1/FVC ratio >0.8 (treatment-by-subgroup interaction p=0.1251).

In conclusion, in *post hoc* analyses of pooled data from the INPULSIS trials, the treatment effect of nintedanib was not influenced by the presence of emphysema or by FEV1/FVC ratio at baseline. These findings are consistent with previous subgroup analyses of the INPULSIS trials showing that the effect of nintedanib is consistent across subgroups of patients by thresholds of FVC at baseline [10, 11] and across subgroups defined based on other baseline characteristics [12–15]. Interpretation of our findings is limited by the lack of an assessment of the extent or distribution of emphysema or fibrosis on HRCT at baseline. Further research is warranted into the potential impact of emphysema on FVC decline in patients with IPF.

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