ORIGINAL ARTICLE

Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across Prespecified Subgroups in INPULSIS

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Abstract

Rationale: In the two replicate, placebo-controlled, 52-week, phase III INPULSIS trials, nintedanib 150 mg twice daily significantly reduced the annual rate of decline in FVC, the primary endpoint, in subjects with idiopathic pulmonary fibrosis (IPF). It is unknown if this effect was uniform across all subjects treated with nintedanib.

Objectives: To investigate the potential association of demographic and clinical variables with the effect of nintedanib in subjects with IPF.

Methods: Subgroup analyses of pooled data from the INPULSIS trials were prespecified. Subgroups were analyzed by sex, age ($<$65, $\geq$65 yr), race (white, Asian), baseline FVC percentage predicted ($\leq$70%, $>$70%), baseline St. George's Respiratory Questionnaire (SGRQ) total score ($\leq$40, $>$40), smoking status (never, ex/current), systemic corticosteroid use (yes/no), and bronchodilator use (yes/no).

Measurements and Main Results: A total of 1,061 subjects were treated (nintedanib n = 638, placebo n = 423). There was no statistically significant difference in the effect of nintedanib for the primary endpoint or the key secondary endpoints of change from baseline in SGRQ total score or time to first acute exacerbation in any subgroup. Treatment effects for the key secondary endpoints seemed more pronounced in subjects with baseline FVC $\leq$70% predicted, because the majority of acute exacerbations and a greater deterioration in SGRQ total score occurred in placebo-treated subjects in this subgroup.

Conclusions: Pooled data from the INPULSIS trials support a consistent effect of nintedanib across a range of IPF phenotypes by slowing disease progression across a number of prespecified subgroups.

Keywords: disease progression; forced vital capacity; quality of life

At a Glance Commentary

Scientific Knowledge on the Subject: Compared with placebo, nintedanib 150 mg twice daily consistently slowed disease progression by significantly reducing the annual rate of decline in FVC, the primary endpoint, in the two, replicate, 52-week phase III INPULSIS trials of subjects with idiopathic pulmonary fibrosis (n = 1,061).

What This Study Adds to the Field: Findings from prespecified subgroup analyses of pooled data from the two INPULSIS trials support a consistent effect of nintedanib on slowing disease progression across subgroups defined by a number of extrinsic and intrinsic variables.

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Table 1. Baseline Characteristics

Characteristics	Nintedanib 150 mg Twice Daily (*n* = 638)	Placebo (*n* = 423)	Total (*n* = 1,061)
Male sex, n (%)	507 (79.5)	334 (79.0)	841 (79.3)
Age, yr, mean (SD)	66.6 (8.1)	67.0 (7.9)	66.8 (8.0)
Weight, kg, mean (SD)	79.2 (16.6)	78.6 (16.5)	79.0 (16.6)
Body mass index, kg/m^2, mean (SD)	28.1 (4.6)	27.6 (4.6)	27.9 (4.6)
Race			
White	360 (56.4)	248 (58.6)	608 (57.3)
Asian	194 (30.4)	128 (30.3)	322 (30.3)
Black	2 (0.3)	0 (0.0)	2 (0.2)
Missing*	82 (12.9)	47 (11.1)	129 (12.2)
Smoking status, n (%)			
Never smoked	174 (27.3)	122 (28.8)	296 (27.9)
Ex-smoker	435 (68.2)	283 (66.9)	718 (67.7)
Current smoker	29 (4.5)	18 (4.3)	47 (4.4)
Time since diagnosis of IPF, yr, mean (SD)	1.7 (1.4)	1.6 (1.3)	1.6 (1.3)
Systemic corticosteroid use, n (%)	136 (21.3)	89 (21.0)	225 (21.2)
Bronchodilator use, n (%)	129 (20.2)	72 (17.0)	201 (18.9)
FVC, ml, mean (SD)	2714 (757)	2728 (810)	2719 (778)
FVC, % predicted, mean (SD)	79.7 (17.6)	79.3 (18.2)	79.6 (17.8)
FEV_1/FVC ratio, %, mean (SD)	81.7 (5.8)	81.7 (6.0)	81.7 (5.9)
D_{LCO}, % predicted, mean (SD)†	47.4 (13.5)	47.0 (13.4)	47.2 (13.5)
Sp_{O_2}, %, mean (SD)	95.9 (2.3)	95.8 (2.0)	95.8 (2.2)
SGRQ total score, mean (SD)‡	39.5 (19.2)	39.6 (18.5)	39.5 (18.9)

Definition of abbreviations: D_{LCO} = diffusing capacity of the lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis; SGRQ = St. George's Respiratory Questionnaire; Sp_{O_2} = oxygen saturation on pulse oximetry.
*It was not permitted to collect data on race in France.
†n = 422 for placebo.
‡n = 624 for nintedanib 150 mg twice daily and n = 419 for placebo.

Idiopathic pulmonary fibrosis (IPF) is a fatal, progressive fibrosing interstitial pneumonia, characterized by dyspnea and decline in lung function (1). The course of IPF is highly variable and difficult to predict in individual patients (2). Recently, two drugs have been shown to slow disease progression in patients with IPF (3, 4) and have been approved by the US Food and Drug Administration, providing a choice of treatments for this devastating disease for the first time.

Nintedanib is an intracellular inhibitor of tyrosine kinases including the fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor receptors (5, 6). Nonclinical studies have shown that nintedanib interferes with processes active in fibrosis, such as fibroblast proliferation, migration and differentiation, and the secretion of the extracellular matrix (6–8). Based on the results of the phase II dose-finding TOMORROW trial, which indicated a reduction in the annual rate of decline in FVC, a lower incidence of acute exacerbations and preservation of health-related quality of life (HRQL) with nintedanib 150 mg twice daily versus placebo (9), the 150-mg twice daily dose of nintedanib was chosen for the phase III INPULSIS trials.

The INPULSIS trials were two replicate randomized, double-blind, placebo-controlled, 52-week phase III trials that assessed the efficacy and safety of nintedanib 150 mg twice daily in subjects with IPF (randomized in a 3:2 ratio to nintedanib and placebo) (4, 10). Treatment interruption and dose reduction from 150 to 100 mg twice daily were allowed for the management of adverse events. Compared with placebo, nintedanib consistently slowed disease progression by significantly reducing the annual rate of decline in FVC in both trials (a difference of 125.3 ml/yr; 95% confidence interval [CI], 77.7–172.8; $P < 0.001$ in INPULSIS-1 and 93.7 ml/yr; 95% CI, 44.8–142.7; $P < 0.001$ in INPULSIS-2).

The key secondary endpoints in the INPULSIS trials were time to first acute exacerbation, as reported by the investigators, and change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score, both over 52 weeks. In INPULSIS-2, there was a significant difference in favor of nintedanib on time to first acute exacerbation over 52 weeks (hazard ratio [HR], 0.38; 95% CI, 0.19–0.77; $P = 0.005$); in INPULSIS-1, there was no significant difference between the nintedanib and placebo groups for this endpoint (HR, 1.15; 95% CI, 0.54–2.42; $P = 0.67$). In INPULSIS-2, there was a significant, albeit modest, difference in favor of nintedanib on change from baseline in SGRQ total score over 52 weeks (2.80 vs. 5.48 for nintedanib vs. placebo, respectively; a difference of −2.69; 95% CI, −4.95 to −0.43; $P = 0.02$), but no difference between groups was observed in INPULSIS-1 (4.34 vs. 4.39 for nintedanib vs. placebo, respectively; a difference of −0.05; 95% CI, −2.50 to 2.40; $P = 0.97$).

To assess the consistency of the effect of nintedanib among subjects with various demographic and clinical variables, a number of subgroup analyses using pooled data from the INPULSIS trials were prespecified, and the results of these analyses are presented here. Some of these results have been reported as abstracts (11–13).

Methods

Prespecified analyses were conducted to evaluate the impact of nintedanib on the primary and two key secondary endpoints in

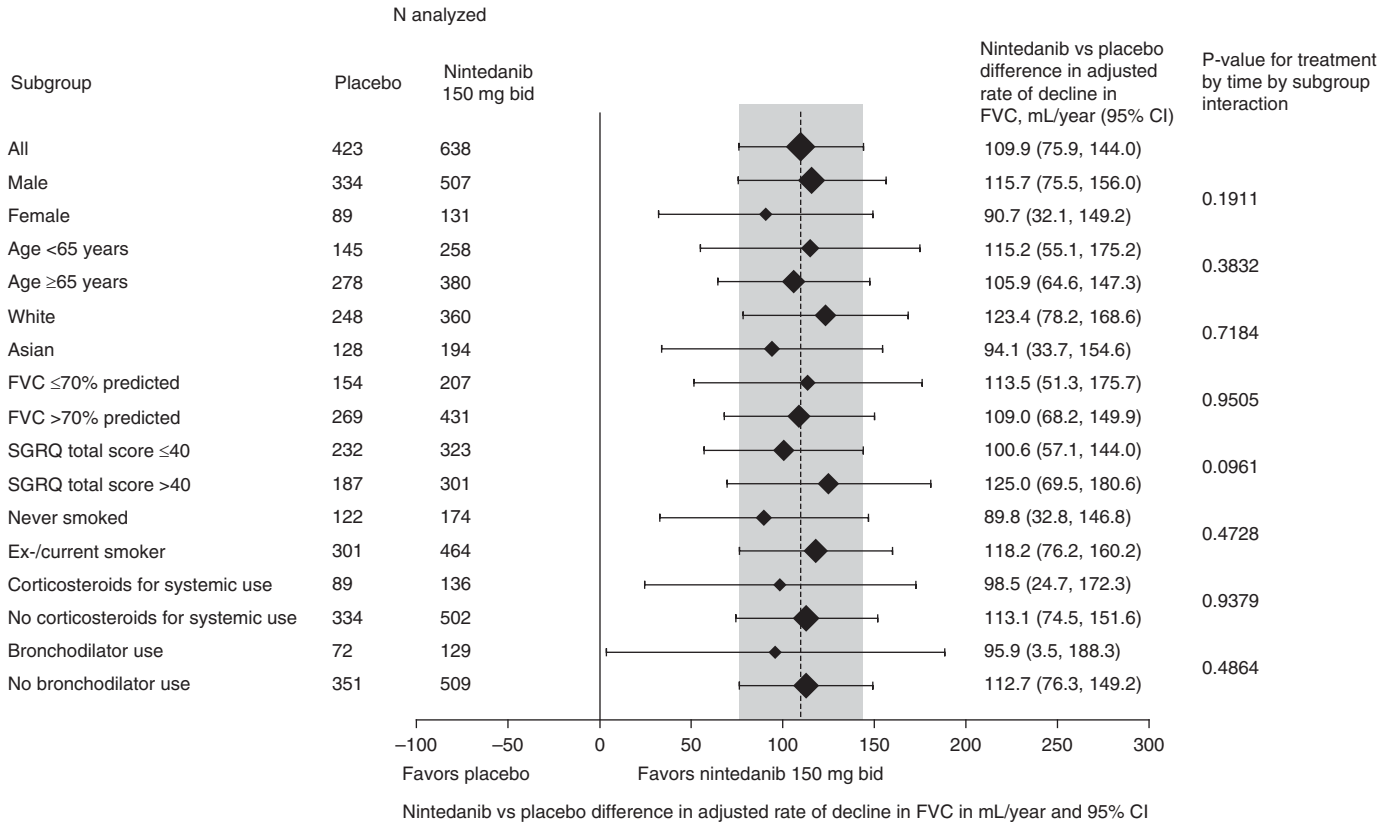


Figure 1. Forest plot for the annual rate of decline in FVC (ml/yr) by subgroup. Based on a random coefficient regression with fixed effects for treatment, sex, age, height, and random effect of subject-specific intercept and time. The *vertical dashed line* and *shaded area* show the point estimate and 95% confidence interval (CI) for the overall pooled population. bid = twice daily; SGRQ = St. George's Respiratory Questionnaire.

subject subgroups using pooled data from the two INPULSIS trials. Despite the heterogeneity of the key secondary endpoint results between the INPULSIS trials, it was considered acceptable to pool the data from both trials for subgroup analyses, as prespecified, because there were no differences in baseline characteristics (except for a higher proportion of Asian subjects in INPULSIS-2) or in the primary outcome between the trials. Subgroups included sex (male, female), age ($<$65, $\geq$65 yr), race (white, Asian), baseline FVC percentage predicted ($\leq$70%, $>$70%), baseline SGRQ total score ($\leq$40, $>$40), smoking status (never, ex/current), systemic corticosteroid use at baseline (yes/no), and bronchodilator use at baseline (yes/no).

In the INPULSIS trials, the annual rate of decline in FVC was analyzed using a random coefficient regression model (with random slopes and intercepts) that included sex, age, and height as covariates. The treatment effect was determined by using estimated slopes for each study group (on the basis of the time-by-treatment interaction term from the random coefficient regression model). All available FVC values from baseline to week 52 were used in the primary model, including FVC measurements at the follow-up visit for subjects who discontinued the study medication prematurely and did not complete study visits until week 52. Using all FVC values collected from baseline to week 52 was considered to be a more robust methodology than using only the FVC values from baseline and week 52, because it enabled calculation of the rate of decline even in subjects without a week 52 value. Change from baseline in SGRQ total score over 52 weeks was analyzed using a mixed model for repeated measures, including treatment and visit as fixed effects, baseline score as a covariate, and treatment-by-visit and baseline-by-visit as interaction terms. The subject effect was assumed to be random. For the time to first acute exacerbation, Kaplan-Meier estimates were derived to calculate the probability of a first acute exacerbation over time. All investigator-reported exacerbations over 52 weeks were taken into account. The estimate and the two-sided asymptotic 95% CI for the HR of nintedanib over placebo was obtained using the Cox's proportional hazards model, and adjusted for sex, baseline height, and baseline age. The *P* value from the log-rank test was also provided. The analyses of pooled data from the trials were the same as for the individual trials, except for the addition of trial as a fixed effect to the statistical models. All significance tests were two-sided, with an α value of 0.05.

For the present study, an assessment of the impact of subgroups was conducted by repeating the primary analysis in each subgroup to estimate the treatment effect within each category. To assess the consistency of the treatment effect across subgroups for the primary endpoint, the terms subgroup and an interaction term treatment-by-time-by-subgroup were added to the main model. From this latter model, the *P* value of the interaction term treatment-by-time-by-subgroup was provided. To assess the consistency of the treatment effect across subgroups for the

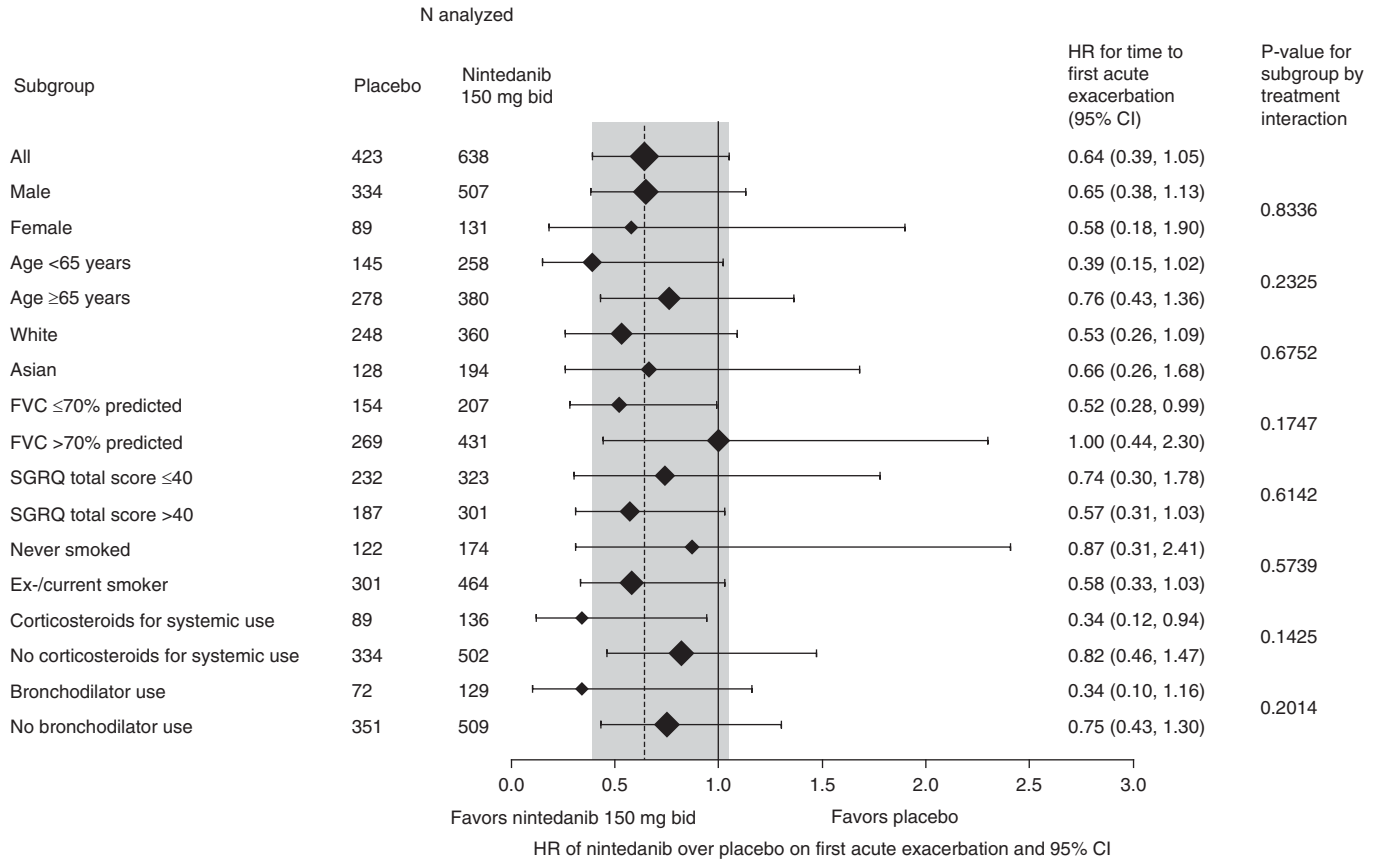


Figure 2. Forest plot for the time to first investigator-reported acute exacerbation over 52 weeks by subgroup. The *vertical dashed line* and *shaded area* show the point estimate and 95% confidence interval (CI) for the overall pooled population. bid = twice daily; HR = hazard ratio; SGRQ = St. George's Respiratory Questionnaire.

key secondary endpoints, the terms subgroup and the interaction term treatment-by-subgroup were added to the main model. From this latter model, the *P* value of the interaction term treatment-by-subgroup was provided. The interaction *P* value is an indicator of the potential differences in treatment effect between the subgroups. No adjustment of *P* values for multiple testing was performed for the subgroup analyses.

Results

Subjects

A total of 1,061 subjects were treated in the two INPULSIS trials (638 in the nintedanib group and 423 in the placebo group). Demographics and baseline characteristics were comparable between the treatment groups (Table 1). Across each of the subgroups, the proportions of subjects generally reflected the 3:2 randomization ratio for nintedanib:placebo in the overall population. However, the number of subjects was relatively small (<90 subjects) in the placebo arms for the subgroups of female sex, corticosteroids for systemic use, and bronchodilator use.

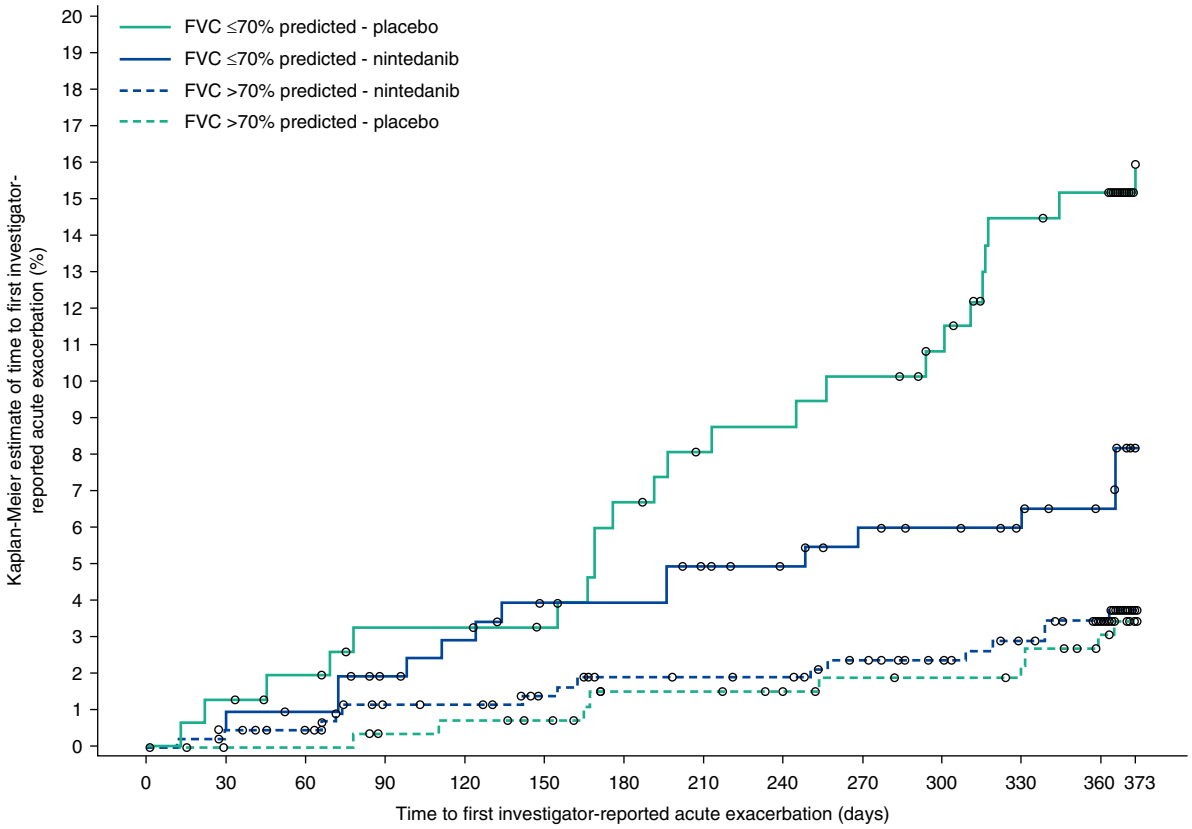
Primary Endpoint

Results of the prespecified subgroup analyses for the annual rate of decline in FVC are presented in Figure 1. Nintedanib demonstrated a consistent treatment effect on the annual rate of decline in FVC across all subgroups. The treatment effect in all subgroups was consistent with the treatment effect in the overall pooled population.

Key Secondary Endpoints

Results of the prespecified subgroup analyses for time to first acute exacerbation are presented in Figure 2. No statistically significant treatment-by-subgroup interaction was observed in any of the subgroup analyses, indicating that the treatment effect of nintedanib was consistent across the subgroups. The consistency of the treatment effect can also be seen in the forest plot, because the CIs estimated for the treatment effects in the subgroups overlap with the CI of the overall treatment effect. The number of subjects with acute exacerbations was generally low, and in some of the subgroups, very few subjects had acute exacerbations. In the subgroup analysis by baseline FVC percentage predicted, acute exacerbations were reported in 7.7% versus 14.9% (16 vs. 23 subjects) of nintedanib- and placebo-treated subjects with baseline FVC ⩽70% predicted (HR, 0.52; 95% CI, 0.28–0.99), and in 3.5% versus 3.3% (15 vs. 9 subjects) of nintedanib- and placebo-treated subjects with baseline FVC >70% predicted (HR, 1.00; 95% CI, 0.44–2.30), respectively (Figure 3).

Results of the prespecified subgroup analyses for change from baseline in SGRQ total score are presented in Figure 4. No



No. of patients

FVC ≤70% predicted – placebo	154	152	148	144	144	142	137	133	132	130	126	118	116	106
FVC ≤70% predicted – nintedanib	207	205	203	198	195	191	190	186	183	179	177	174	169	160
FVC >70% predicted – nintedanib	431	427	424	411	410	404	399	398	397	391	385	379	368	332
FVC >70% predicted – placebo	269	267	267	264	263	261	256	256	254	251	250	249	243	235

Figure 3. Time to first investigator-reported acute exacerbation over 52 weeks in subgroups by baseline FVC ⩽70% versus >70% predicted. Treatment-by-subgroup interaction $P = 0.1747$; hazard ratios were 0.52 (95% confidence intervals, 0.28–0.99) and 1.00 (95% confidence intervals 0.44–2.30) for the baseline FVC ⩽70% predicted and baseline FVC >70% predicted subgroups, respectively.

significant treatment-by-subgroup interaction was observed in any of the subgroup analyses. There appeared to be a more pronounced treatment effect in subjects with baseline FVC ⩽70% predicted (Figure 5), in female subjects, and in subjects using a bronchodilator at baseline. This was due to a greater mean increase (deterioration) from baseline in SGRQ total score in subjects with baseline FVC ⩽70% predicted (n = 150) than in subjects with baseline FVC >70% predicted (n = 263) (6.86 vs. 3.90), in female subjects (n = 85) than in male subjects (n = 328) (7.41 vs. 4.31), and in subjects using a bronchodilator (n = 68) versus subjects not using a bronchodilator at baseline (n = 345) (9.27 vs. 4.31) in the placebo group. It should be noted that differences in SGRQ total score at baseline were also apparent for subjects with baseline FVC ⩽70% versus >70% predicted (45.44 vs. 36.47), female versus male subjects (44.30 vs. 38.33), and subjects using a bronchodilator versus not using a bronchodilator at baseline (48.04 vs. 37.58).

Discussion

In the two replicate phase III INPULSIS trials, as well as in the dose-finding phase II TOMORROW trial (9), nintedanib 150 mg twice daily consistently demonstrated a slowing of disease progression versus placebo in subjects with IPF. The prespecified subgroup analyses presented in this study showed that a consistent effect of nintedanib on disease progression was observed across subgroups of subjects that were defined based on a variety of demographic and clinical factors. This indicates that nintedanib is effective across a wide range of phenotypes in IPF.

The subgroup analysis methodology used in the INPULSIS trials follows the recommendations in the European Medicines Agency draft guidance on the investigation of subgroups in confirmatory trials (14). Treatment-by-subgroup interaction *P* values were produced to highlight potential subgroups with differential effects. Because the INPULSIS studies were not designed specifically to assess the treatment effect of nintedanib in subgroups, the interaction tests were likely underpowered, and as such, lack of significance did not necessarily imply the absence of a true, underlying difference

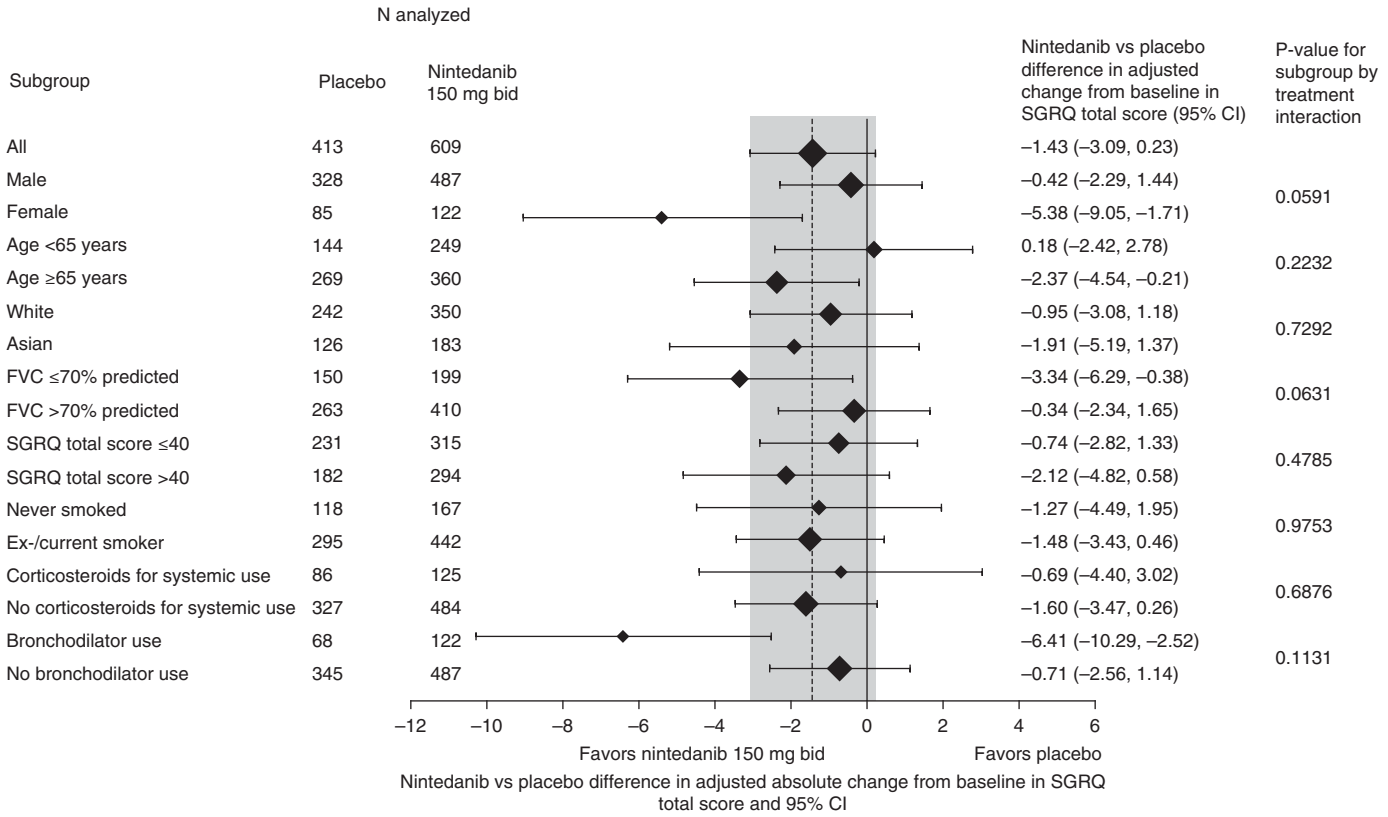


Figure 4. Forest plot for the change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 52 weeks by subgroup. The *vertical dashed line* and *shaded area* show the point estimate and 95% confidence interval (CI) for the overall pooled population. bid = twice daily.

between the subgroups. To alleviate this issue, the overlap between the estimated treatment effect in the subgroups and the overall treatment effect was assessed. Some subgroups in which differences were observed, although the interaction test was not significant, are discussed in the following, by describing the results for each treatment group within the subgroups and/or by discussing biological plausibility or limitations.

It has previously been reported that patients with IPF who have better preserved lung function may have a better response to treatment with pirfenidone (15), but this was not observed in our data, which showed no difference in the effect of nintedanib between the subgroups defined by FVC percentage predicted at baseline.

In a pooled analysis of data from both INPULSIS trials, the HR for time to first acute exacerbation was 0.64 (95% CI, 0.39–1.05) in favor of nintedanib ($P = 0.08$) (4). Results of a prespecified sensitivity analysis based on confirmed or suspected acute exacerbations (as per adjudication by a blinded adjudication committee) using pooled data from both trials demonstrated that nintedanib had a significant benefit versus placebo (HR, 0.32; 95% CI, 0.16–0.65; $P = 0.001$) (4). Together with the results of the phase II TOMORROW study, in which nintedanib 150 mg twice daily reduced the risk of acute exacerbations compared with placebo (HR, 0.16; 95% CI, 0.04–0.71) (16), these results support a potential benefit of nintedanib in reducing the risk of acute exacerbations. Although time to first investigator-reported acute exacerbation based on pooled data for the overall population did not reach statistical significance, it was considered appropriate to perform the prespecified subgroup analyses on this endpoint, because there was a numerical difference in favor of nintedanib. There was no significant treatment-by-subgroup interaction for time to first acute exacerbation in any subgroup assessed. Of note, subjects with baseline FVC ⩽70% predicted had a higher incidence of acute exacerbations than subjects with baseline FVC >70% predicted, and the results for the time to first acute exacerbation seemed to be more pronounced in favor of nintedanib in the subgroup with greater lung function impairment. It has been reported that patients with more severe reductions in FVC are at greater risk of acute exacerbation, and our findings are consistent with these data (17, 18). Our findings suggest that nintedanib may be more likely to provide a benefit on reducing the risk of acute exacerbations in individuals with more severe lung function impairment who are at greater risk of such events, and in individuals with systemic corticosteroid use at baseline, but the number of subjects with acute exacerbations in this study was too small to enable firm conclusions to be drawn for individual subgroups.

There was no significant treatment-by-subgroup interaction for change from baseline in SGRQ score in any of the assessed subgroups. As seen for time to acute exacerbation, the treatment effect of nintedanib on HRQL seemed to be more pronounced in subjects with more advanced lung function impairment. It may be

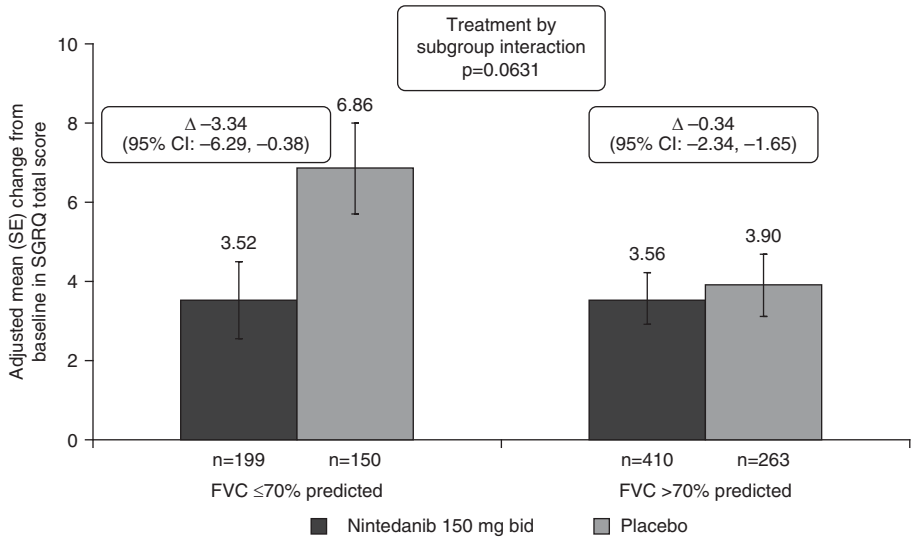


Figure 5. Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at week 52 in subgroups by baseline FVC ⩽70% versus >70% predicted. Mean (SD) SGRQ total score at baseline was 45.7 (17.6) in the nintedanib group and 45.0 (18.7) in the placebo group for the baseline FVC ⩽70% predicted subgroup and 36.5 (19.2) in the nintedanib group and 36.4 (17.7) in the placebo group for the baseline FVC >70% predicted subgroup. bid = twice daily; CI = confidence interval.

hypothesized that change in SGRQ total score is a more sensitive tool to detect changes in lung volume in individuals with more advanced impairment of lung function, because these individuals have a greater reduction of their respiratory reserve. It seems intuitive that the same decline in FVC translates into a greater change in SGRQ total score in individuals with more advanced disease than in individuals with less advanced disease and a better SGRQ total score at baseline. The treatment effect also seemed to be more pronounced in women than men. In a study that examined differences in measures of HRQL between male and female subjects with IPF, male subjects reported worse physical HRQL but better emotional HRQL than female subjects, which suggested that interventions might have different effects between the sexes (19). However, the apparent differences in treatment effect in our study appear to be driven by the varying magnitude of change from baseline in SGRQ score in placebo-treated subjects within these subgroups. It should also be taken into account that interpretation of these findings is limited by the low number of subjects in some of the subgroups, and that although there is evidence to support the use of the SGRQ as a measure of HRQL in individuals with IPF, it requires further validation in this population (20).

The subgroup analyses presented here, as well as further *post hoc* subgroup analyses by presence of emphysema at baseline, baseline FVC ⩽90% versus >90% predicted, and high-resolution computed tomography diagnostic criteria (21–23) did not identify a particular group of subjects for whom the treatment effect of nintedanib was significantly better or worse compared with the overall population. Nintedanib has been approved for the treatment of IPF without restriction based on physiological criteria in the United States, the European Union, and Japan (16, 24). To date, no physiological measure or biomarker predicting responsiveness to treatment with nintedanib in IPF has been identified. Further research is needed to identify biomarkers or other factors that predict response to treatment with nintedanib in individuals with IPF.

In conclusion, analyses of pooled data from the INPULSIS trials support a consistent effect of nintedanib across a range of IPF patient phenotypes, by slowing disease progression across a number of prespecified subgroups. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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