

Nintedanib and Sildenafil in Patients with Idiopathic Pulmonary Fibrosis and Right Heart Dysfunction

A Prespecified Subgroup Analysis of a Double-Blind Randomized Clinical Trial (INSTAGE)

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Abstract

Rationale: In the INSTAGE trial in patients with idiopathic pulmonary fibrosis (IPF) and severely impaired gas exchange, nintedanib plus sildenafil was associated with numerical benefits on St. George's Respiratory Questionnaire (SGRQ) total score, brain natriuretic peptide (BNP), and FVC decline versus nintedanib alone. Exploratory analyses of the STEP-IPF (Sildenafil Trial of Exercise Performance in IPF) trial suggested that sildenafil may have a greater effect on SGRQ score in patients with IPF who have right heart dysfunction (RHD).

Objectives: Assess whether RHD influenced the effects of nintedanib plus sildenafil versus nintedanib alone in the INSTAGE trial.

Methods: Subgroup analyses of patients with ($n = 117$) versus those without ($n = 156$) echocardiographic signs of RHD at baseline.

Measurements and Main Results: There was no heterogeneity between subgroups by presence of RHD in the effect of nintedanib plus sildenafil versus nintedanib alone on change in SGRQ total

score at Week 12 ($P = 0.74$) or Week 24 ($P = 0.90$), or change in FVC at Week 12 ($P = 0.58$) or Week 24 ($P = 0.55$). In both subgroups, nintedanib plus sildenafil had a numerically greater effect on reducing FVC decline versus nintedanib alone. Between-group differences in change in BNP at Week 24 were -119.9 ng/L (95% confidence interval = -171.3 to -68.5) and -3.6 ng/L (95% confidence interval = -47.2 to 40.0) in patients with and without signs of RHD at baseline, respectively ($P < 0.01$).

Conclusions: In the INSTAGE trial, there were no significant differences in the effects of nintedanib plus sildenafil versus nintedanib alone on changes in SGRQ and FVC between patients with or without echocardiographic signs of RHD at baseline. The benefit of combination therapy on stabilizing BNP was more pronounced in patients with RHD at baseline.

Clinical trial registered with www.clinicaltrials.gov (NCT02802345).

Keywords: pulmonary hypertension; interstitial lung disease; right ventricular function; tyrosine kinase inhibitor

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At a Glance Commentary

Scientific Knowledge on the

Subject: *Post hoc* analyses of data from the STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) trial in patients with idiopathic pulmonary fibrosis and $DL_{CO} < 35\%$ predicted suggested that sildenafil may be associated with benefits on health-related quality of life versus placebo in patients with right heart dysfunction (RHD) on echocardiogram. In the INSTAGE trial in patients with idiopathic pulmonary fibrosis and DL_{CO} of 35% predicted or less, nintedanib plus sildenafil was associated with numerical, but not statistically significant, benefits on St. George's Respiratory Questionnaire total score and FVC versus nintedanib alone.

What This Study Adds to the Field:

Subgroup analyses of data from the INSTAGE trial demonstrate that there was no significant difference in the treatment effect of nintedanib plus sildenafil versus nintedanib alone on change in St. George's Respiratory Questionnaire total score or FVC over 24 weeks between subgroups with and without echocardiographic signs of RHD. The benefit of nintedanib plus sildenafil versus nintedanib alone on stabilizing levels of brain natriuretic peptide, a marker of right ventricular strain, was more pronounced in patients with than in those without echocardiographic signs of RHD.

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing interstitial lung disease (ILD), associated with lung function decline, dyspnea, and impaired health-related quality of life (HRQL) (1, 2). IPF is believed to be the result of recurrent epithelial injury and abnormal repair processes, which lead to excess accumulation of extracellular matrix produced by fibroblasts and myofibroblasts (3, 4). In addition, destruction of the vasculature and aberrant vascular remodeling result in pulmonary vascular abnormalities, particularly in patients with more advanced disease (5, 6).

Nintedanib, an intracellular inhibitor of tyrosine kinases (7), is an approved treatment for IPF. In patients with IPF and mild or moderate impairment in lung function, nintedanib slows disease progression by reducing the annual rate of decline in FVC by about 50% compared with placebo (8, 9). Sildenafil, a phosphodiesterase-5 inhibitor and selective pulmonary vasodilator (10), is an approved treatment for pulmonary arterial hypertension. In the STEP-IPF (Sildenafil Trial of Exercise Performance in IPF) trial in patients with IPF and $DL_{CO} < 35\%$ predicted, there was no significant benefit on exercise capacity with sildenafil versus placebo over 12 weeks, but differences in DL_{CO} , dyspnea, and HRQL favored sildenafil (11). In a *post hoc* analysis, sildenafil was associated with benefits on exercise capacity and HRQL in patients with right ventricular systolic dysfunction (RVSD) or right ventricular hypertrophy (RVH) on echocardiogram (12). In the INSTAGE trial, patients with IPF and DL_{CO} of 35% predicted or lower were randomized to receive nintedanib plus sildenafil or nintedanib alone for 24 weeks, stratified by the presence of echocardiographic signs of right heart dysfunction (RHD) (13). Compared with nintedanib alone, nintedanib plus sildenafil was associated with a numerical, but not statistically significant, benefit on St. George's Respiratory Questionnaire (SGRQ) total score at Week 12 (primary endpoint). Exploratory analyses suggested that treatment with nintedanib plus sildenafil versus nintedanib alone was associated with a reduction in FVC decline and stabilization in brain natriuretic peptide (BNP), a marker of right ventricular strain (13). In this study, we investigated whether the presence of echocardiographic signs of RHD at baseline influenced the effects of nintedanib plus sildenafil versus nintedanib alone in the INSTAGE trial.

Methods

The design of the INSTAGE trial has been described previously (13). Briefly, patients with IPF, DL_{CO} of 35% predicted or lower, and an FEV_1 of 0.7 or greater (prebronchodilator) were randomized 1:1 to receive nintedanib 150 mg twice a day plus sildenafil 20 mg three times a day or nintedanib 150 mg twice a day plus

placebo for 24 weeks, with a follow-up visit 4 weeks later. Patients with symptomatic orthostatic hypotension (systolic blood pressure < 100 mm Hg and/or diastolic blood pressure < 50 mm Hg), uncontrolled systemic hypertension (systolic blood pressure > 180 mm Hg and/or diastolic blood pressure > 100 mm Hg), aortic stenosis or idiopathic hypertrophic subaortic stenosis, or severe chronic heart failure (left ventricular ejection fraction $< 25\%$) at screening were excluded. The primary endpoint was change from baseline in SGRQ total score at Week 12.

In the current analyses, changes from baseline in SGRQ total score, University of California San Diego, Shortness of Breath Questionnaire (UCSD-SOBQ) score, and FVC (ml) at Weeks 12 and 24, change from baseline in BNP at Week 24, time to absolute decline in FVC of 5% predicted or greater or death, and time to relative decline in FVC of 10% predicted or greater or death were assessed in subgroups by the presence/absence of one or more echocardiographic sign(s) of RHD at baseline. Echocardiographic signs of RHD were defined as RVSD, RVH, right ventricular dilatation, paradoxical septum motion, or right atrium enlargement, based on the investigator's judgement (without central review). The procedure for defining RHD and the categories within it based on echocardiography was not mandated in the protocol, but the investigator was asked to report which (if any) of these five echocardiographic signs of RHD was present at baseline. In addition, changes from baseline in BNP at Week 24 were assessed in patients with less than or equal to versus greater than the median level of BNP at baseline.

Changes from baseline in SGRQ total score, UCSD-SOBQ score, and FVC (ml) at Weeks 12 and 24, and in BNP at Week 24, were analyzed based on a mixed model for repeated measures, with fixed effects for the baseline value of the endpoint in question-by-visit and treatment-by-visit-by-subgroup. The rate of decline in FVC over 24 weeks was based on a random coefficient regression with fixed effects for treatment-by-time, sex, age, height, baseline FVC, and random effect of patient-specific intercept and time. Time to absolute decline in FVC of 5% predicted or greater or death, and time to relative decline in FVC of 10% predicted or greater or death were based on a Cox regression model with term

for treatment. In the subgroup analyses, interaction *P* values were calculated to assess potential differences in the treatment effect of nintedanib plus sildenafil versus nintedanib alone between the subgroups. In the analysis of the rate of decline in FVC over 24 weeks, treatment-by-time interaction was replaced by treatment-by-subgroup-by-time interaction in the model. For time to absolute decline in FVC of 5% predicted or greater or death, and time to relative decline in FVC of 10% predicted or greater or death, subgroup and treatment-by-subgroup were included in the model. Analyses were not adjusted for multiplicity.

Safety was assessed via the recording of adverse events with onset between the first dose and up to 28 days after the last dose of trial medication, and coded using the Medical Dictionary for Regulatory Activities

version 21.0. Analyses of safety data were descriptive.

Changes from baseline in SGRQ total score at Weeks 12 and 24 in subgroups by the presence/absence of echocardiographic signs of RHD were prespecified. The other analyses presented in this article were conducted *post hoc*. All analyses were conducted on data from patients who received one or more doses of study drug.

Results

Patients

Of 273 patients treated, 117 patients (61 treated with nintedanib plus sildenafil, 56 treated with nintedanib alone) had echocardiographic signs of RHD at baseline, and 156 patients (76 treated with nintedanib plus sildenafil, 80 treated with nintedanib

alone) did not. The proportions of patients with RVSD, RVH, right ventricular dilatation, paradoxical septum motion, and right atrium enlargement are summarized in Table E1 in the online supplement. Baseline characteristics were generally similar between the subgroups, but higher proportions of patients with signs of RHD were white and had been treated with nintedanib before entering the trial, and baseline levels of BNP were higher in patients with than in those without signs of RHD (Table 1).

HRQL

Between-group differences in change from baseline in SGRQ total score at Week 12 were -0.01 (95% confidence interval [CI] = -4.41 to 4.40) in patients with and -0.96 (95% CI = -4.65 to 2.72) in patients without signs of RHD at baseline (Figure 1A). Between-group differences in

Table 1. Baseline Characteristics by the Presence/Absence of Echocardiographic Signs of RHD at Baseline

Characteristics	Echocardiographic Signs of RHD		No Echocardiographic Signs of RHD	
	Nintedanib + Sildenafil (<i>n</i> = 61)	Nintedanib + Placebo (<i>n</i> = 56)	Nintedanib + Sildenafil (<i>n</i> = 76)	Nintedanib + Placebo (<i>n</i> = 80)
Age, yr, mean (SD)	71.6 (8.9)	71.6 (7.4)	69.2 (8.3)	68.8 (8.0)
Male, <i>n</i> (%)	48 (78.7)	46 (82.1)	62 (81.6)	60 (75.0)
Weight, kg, mean (SD)	75.4 (17.7)	75.8 (16.5)	72.3 (17.7)	73.1 (14.9)
BMI, kg/m ² , mean (SD)	26.6 (5.4)	26.5 (4.7)	25.8 (4.7)	26.5 (4.7)
Race, <i>n</i> (%)				
White	52 (85.2)	48 (85.7)	51 (67.1)	47 (58.8)
Asian	7 (11.5)	7 (12.5)	23 (30.3)	32 (40.0)
Other	2 (3.3)	1 (1.8)	2 (2.6)	1 (1.3)
Time since diagnosis of IPF, yr, mean (SD)	2.3 (1.9)	2.1 (2.0)	2.2 (1.8)	2.1 (1.6)
Emphysema, <i>n</i> (%) [*]	23 (37.7)	20 (35.7)	28 (36.8)	25 (31.3)
Smoking status, <i>n</i> (%)				
Never smoker	14 (23.0)	7 (12.5)	19 (25.0)	20 (25.0)
Ex-smoker	46 (75.4)	46 (82.1)	54 (71.1)	57 (71.3)
Current smoker	1 (1.6)	3 (5.4)	3 (3.9)	3 (3.8)
Nintedanib status at entry into trial, <i>n</i> (%)				
Naive	29 (47.5)	34 (60.7)	47 (61.8)	53 (66.3)
Currently treated	29 (47.5)	20 (35.7)	27 (35.5)	26 (32.5)
Previously treated	3 (4.9)	2 (3.6)	2 (2.6)	1 (1.3)
FVC, ml, mean (SD)	2,257 (771)	2,232 (710)	2,236 (735)	2,146 (837)
FVC, % predicted, mean (SD)	68.7 (20.2)	66.4 (16.4)	67.4 (18.6)	65.8 (20.3)
DL _{CO} , % predicted, mean (SD) [†]	25.0 (7.0)	23.9 (7.0)	26.4 (6.7)	26.8 (6.8)
SGRQ total score, mean (SD) [‡]	58.4 (18.0)	57.3 (18.2)	55.3 (18.9)	51.7 (17.5)
UCSD-SOBQ score, mean (SD) [§]	64.2 (25.7)	63.5 (23.1)	57.4 (26.2)	52.3 (25.6)
BNP, ng/L, mean (SD)	164.7 (292.2)	174.0 (243.9)	58.2 (48.5)	63.4 (57.1)

Definition of abbreviations: BMI = body mass index; BNP = brain natriuretic peptide; IPF = idiopathic pulmonary fibrosis; RHD = right heart dysfunction; SGRQ = St. George's Respiratory Questionnaire; UCSD-SOBQ = University of California San Diego, Shortness of Breath Questionnaire.

^{*}Determined by the investigator based on qualitative assessment of high-resolution computed tomography scans.

[†]*n* = 79 for nintedanib + placebo in no echocardiographic signs of RHD subgroup.

[‡]*n* = 60 for nintedanib + sildenafil and *n* = 54 for nintedanib + placebo in echocardiographic signs of RHD subgroup; *n* = 76 for nintedanib + sildenafil and *n* = 79 for nintedanib + placebo in no echocardiographic signs of RHD subgroup.

[§]*n* = 55 for nintedanib + sildenafil and *n* = 47 for nintedanib + placebo in echocardiographic signs of RHD subgroup; *n* = 72 for nintedanib + sildenafil and *n* = 79 for nintedanib + placebo in no echocardiographic signs of RHD subgroup.

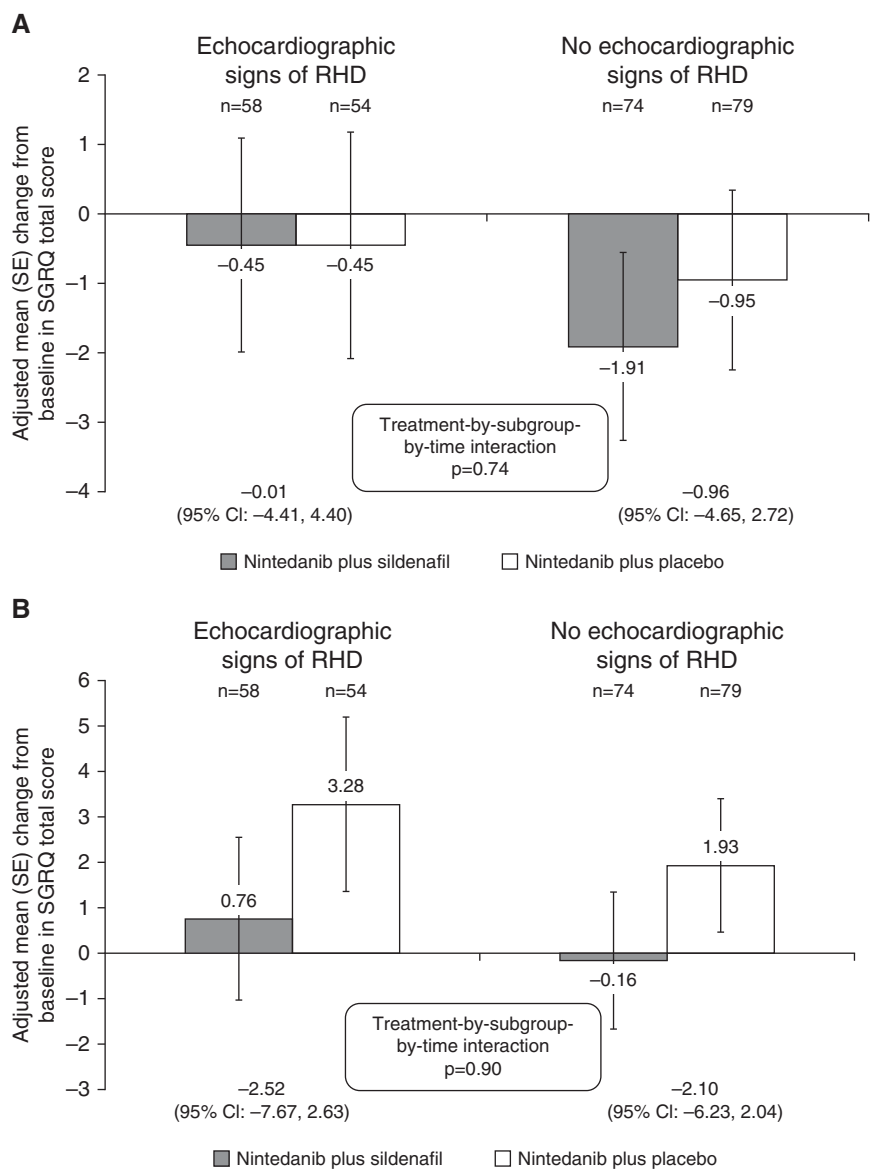


Figure 1. Changes from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at (A) Week 12 and (B) Week 24 by the presence/absence of echocardiographic signs of right heart dysfunction (RHD) at baseline. CI = confidence interval.

changes in SGRQ total score at Week 24 were -2.52 (95% CI = -7.67 to 2.63) in patients with and -2.10 (95% CI = -6.23 to 2.04) in patients without signs of RHD at baseline (Figure 1B). There was no heterogeneity between subgroups in the treatment effect of nintedanib plus sildenafil versus nintedanib alone based on changes at Week 12 ($P=0.74$) or Week 24 ($P=0.90$). Changes in SGRQ total score over time are presented in Figure E1. The treatment effect of nintedanib plus sildenafil versus nintedanib alone on SGRQ total score was also generally consistent

between subgroups defined by the presence/absence of RVSD, RVH, right ventricular dilatation, paradoxical septum motion, or right atrium enlargement, at baseline (see Tables E2–E6).

Between-group differences in change from baseline in UCSD-SOBQ score at Week 12 were -4.28 (95% CI = -11.43 to 2.88) in patients with and -2.06 (95% CI = -7.54 to 3.41) in patients without signs of RHD at baseline. Between-group differences in changes in UCSD-SOBQ score at Week 24 were -2.90 (95% CI = -11.17 to 5.37) in patients with and

-1.54 (95% CI = -7.84 to 4.75) in patients without signs of RHD at baseline. There was no heterogeneity between subgroups in the treatment effect of nintedanib plus sildenafil versus nintedanib alone based on changes at Week 12 ($P=0.63$) or Week 24 ($P=0.80$).

Lung Function

In the overall trial population, nintedanib plus sildenafil had a numerically greater effect than nintedanib alone on change in FVC (between-group difference, 32.5 ml [95% CI = -11.6 to 76.6]) at Week 12 and 37.4 ml (95% CI = -17.4 to 92.3) at Week 24. Between-group differences in change from baseline in FVC at Week 12 were 47.7 ml (95% CI = -20.3 to 115.6) in patients with and 22.4 ml (95% CI = -35.5 to 80.2) in patients without signs of RHD at baseline (Figure 2A). Between-group differences in change from baseline in FVC at Week 24 were 58.0 ml (95% CI = -27.5 to 143.5) in patients with and 24.5 ml (95% CI = -47.0 to 96.0) in patients without signs of RHD at baseline (Figure 2B). There was no heterogeneity between subgroups in the treatment effect of nintedanib plus sildenafil versus nintedanib alone at either time point ($P=0.58$ and $P=0.55$, respectively).

In patients with signs of RHD at baseline, adjusted rates of decline in FVC were 22.9 ml/24 weeks in the nintedanib plus sildenafil group and -63.3 ml/24 weeks in patients who received nintedanib alone (difference, 86.2 ml/24 wk [95% CI = -2.7 to 175.0]). In patients without signs of RHD at baseline, adjusted rates of decline in FVC were -50.9 ml/24 weeks in the nintedanib plus sildenafil group and -69.8 ml/24 weeks in patients who received nintedanib alone (difference, 19.0 ml/24 wk [95% CI = -51.0 to 88.9]). There was no heterogeneity between subgroups in the treatment effect of nintedanib plus sildenafil versus nintedanib alone ($P=0.29$).

The hazard ratio for time to absolute decline in FVC of 5% predicted or greater or death was 0.72 (95% CI = 0.41 – 1.27) in patients with and 0.46 (95% CI = 0.27 – 0.78) in patients without signs of RHD at baseline, both in favor of nintedanib plus sildenafil (Table 2 and Figure E2). No heterogeneity between subgroups was observed in the treatment effect of nintedanib plus sildenafil versus

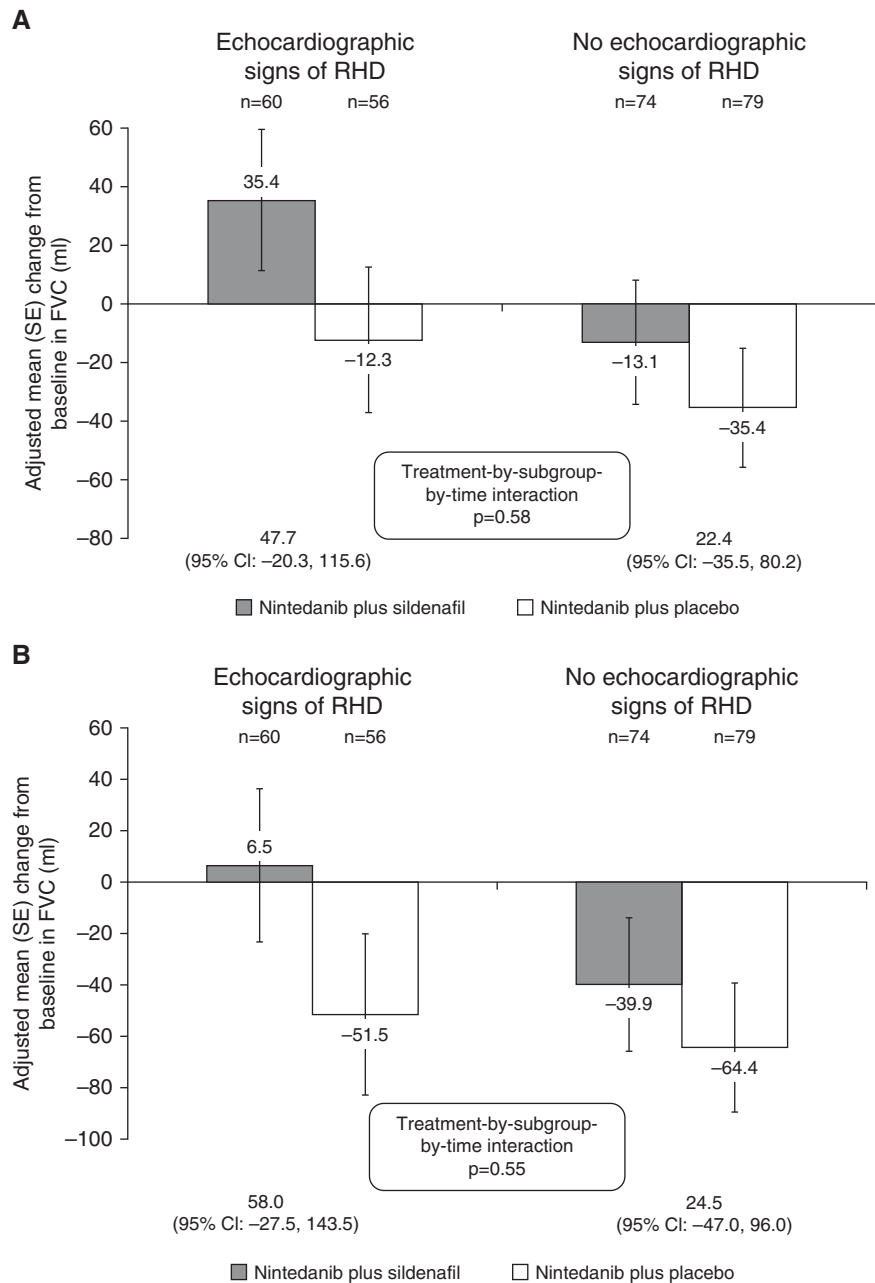


Figure 2. Changes from baseline in FVC (ml) at (A) Week 12 and (B) Week 24 by the presence/absence of echocardiographic signs of right heart dysfunction (RHD) at baseline. CI = confidence interval.

nintedanib alone ($P = 0.28$). The hazard ratio for time to relative decline in FVC of 10% predicted or greater or death was 0.71 (95% CI = 0.38–1.34) in patients with and 0.66 (95% CI = 0.36–1.19) in patients without signs of RHD at baseline, both in favor of nintedanib plus sildenafil (Table 2 and Figure E3). No heterogeneity between subgroups was observed in the treatment effect of

nintedanib plus sildenafil versus nintedanib alone ($P = 0.90$).

BNP

In patients with signs of RHD at baseline, mean BNP at baseline was 164.7 ng/L and 174.0 ng/L in patients treated with nintedanib plus sildenafil and nintedanib alone, respectively. Adjusted mean changes from baseline in BNP at Week 24 in this subgroup were -18.3 ng/L

in patients who received nintedanib plus sildenafil and 101.6 ng/L in patients who received nintedanib alone (difference, -119.9 ng/L [95% CI = -171.3 to -68.5]). In patients without signs of RHD at baseline, mean BNP at baseline was 58.2 ng/L and 63.4 ng/L, and adjusted mean changes in BNP at Week 24 were -6.6 ng/L and -3.0 ng/L in patients treated with nintedanib plus sildenafil and nintedanib alone, respectively (difference, -3.6 ng/L [95% CI = -47.2 to 40.0]; Figure 3). The treatment effect of nintedanib plus sildenafil versus nintedanib alone on change in BNP was significantly greater in patients with than without signs of RHD at baseline ($P < 0.01$). Subgroup analyses of patients with or without RVSD, RVH, right ventricular dilatation, paradoxical septum motion, or right atrium enlargement also showed that the treatment effect of nintedanib plus sildenafil versus nintedanib alone was greater in patients with than without these abnormalities (see Tables E7–E11).

Median BNP at baseline was 52 ng/L. A total of 140 patients (79 treated with nintedanib plus sildenafil and 61 treated with nintedanib alone) had a BNP of 52 ng/L or less and 133 patients (58 treated with nintedanib plus sildenafil and 75 treated with nintedanib alone) had a BNP >52 ng/L at baseline. In patients with a BNP of 52 ng/L or less at baseline, adjusted mean changes from baseline in BNP at Week 24 were -5.4 ng/L and -0.7 ng/L in patients treated with nintedanib plus sildenafil and nintedanib alone, respectively (difference, -4.7 ng/L [95% CI = -50.9 to 41.5]). In patients with a BNP >52 ng/L at baseline, adjusted mean changes from baseline in BNP at Week 24 were -20.4 ng/L and 73.0 ng/L in patients treated with nintedanib plus sildenafil and nintedanib alone, respectively (difference, -93.4 ng/L [95% CI = -142.1 to -44.7]; see Figure E4). The treatment effect of nintedanib plus sildenafil versus nintedanib alone was significantly greater in patients with a BNP greater than 52 ng/L than in patients with a BNP of 52 ng/L or less at baseline ($P = 0.01$).

Adverse Events

A summary of adverse events in subgroups by echocardiographic signs of RHD at baseline is presented in Table 3. Among

Table 2. Time to Absolute Decline in FVC of 5% Predicted or Greater or Death, or Relative Decline in FVC of 10% Predicted or Greater or Death, by the Presence/Absence of Echocardiographic Signs of RHD at Baseline

	Echocardiographic Signs of RHD		No Echocardiographic Signs of RHD	
	Nintedanib + Sildenafil (n = 61)	Nintedanib + Placebo (n = 56)	Nintedanib + Sildenafil (n = 76)	Nintedanib + Placebo (n = 80)
Absolute decline in FVC \geq 5% predicted or death, n (%)	22 (36.1)	27 (48.2)	21 (27.6)	42 (52.5)
Absolute decline in FVC \geq 5% predicted only, n	13	20	16	34
Death only, n	8	3	4	6
Absolute decline in FVC \geq 5% predicted and death, n	1	4	1	2
HR (95% CI)	0.72 (0.41–1.27)		0.46 (0.27–0.78)	
Treatment-by-subgroup interaction			P = 0.28	
Relative decline in FVC \geq 10% predicted or death, n (%)	17 (27.9)	22 (39.3)	18 (23.7)	28 (35.0)
Relative decline in FVC \geq 10% predicted only, n	8	15	13	20
Death only, n	7	4	5	7
Relative decline in FVC \geq 10% predicted and death, n	2	3	0	1
HR (95% CI)	0.71 (0.38–1.34)		0.66 (0.36–1.19)	
Treatment-by-subgroup interaction			P = 0.90	

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; RHD = right heart dysfunction.

patients treated with nintedanib plus sildenafil, serious adverse events were reported in 23.0% and 30.3% of patients, and fatal adverse events in 11.5% and 6.6%

of patients, with and without signs of RHD at baseline, respectively. Among patients treated with nintedanib alone, serious adverse events were reported in 37.5% and

28.8% of patients, and fatal adverse events in 10.7% and 7.5% of patients, with and without signs of RHD at baseline, respectively.

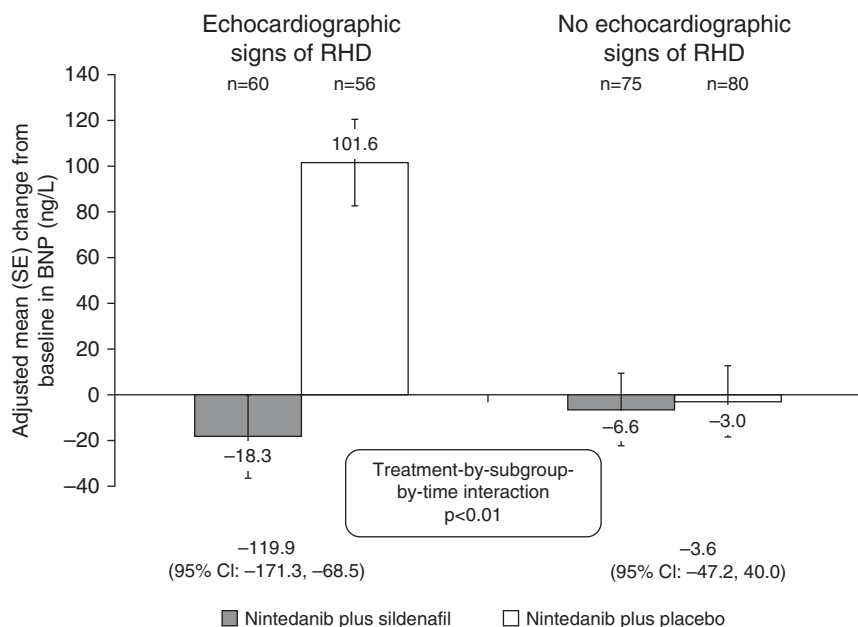


Figure 3. Changes from baseline in brain natriuretic peptide (BNP) at Week 24 by the presence/absence of echocardiographic signs of right heart dysfunction (RHD) at baseline. CI = confidence interval.

Discussion

In the INSTAGE trial, conducted in patients with IPF and severely impaired gas exchange, there was no significant difference in the treatment effect of nintedanib plus sildenafil versus nintedanib alone on change in SGRQ total score over 12 or 24 weeks between subgroups by the presence/absence of RHD (or RVSD or RVH) at baseline. This finding is in contrast to exploratory data from the STEP-IPF trial, based on a small number of patients in whom echocardiograms were centrally reviewed, in which sildenafil was associated with a benefit versus placebo on SGRQ score over 12 weeks in patients with IPF who had RVSD at baseline ($n = 22$) (12).

The presence of echocardiographic signs of RHD at baseline did not influence the effect of nintedanib plus sildenafil versus nintedanib alone on reducing FVC decline over 12 or 24 weeks: nintedanib plus sildenafil had a numerically greater effect on

Table 3. Adverse Events by the Presence/Absence of Echocardiographic Signs of RHD at Baseline

	Echocardiographic Signs of RHD		No Echocardiographic Signs of RHD	
	Nintedanib + Sildenafil (n = 61)	Nintedanib + Placebo (n = 56)	Nintedanib + Sildenafil (n = 76)	Nintedanib + Placebo (n = 80)
Any adverse event(s)	60 (98.4)	53 (94.6)	73 (96.1)	74 (92.5)
Most frequent adverse event(s)*				
Diarrhea	36 (59.0)	24 (42.9)	43 (56.6)	42 (52.5)
Decreased appetite	13 (21.3)	12 (21.4)	7 (9.2)	11 (13.8)
Nausea	12 (19.7)	8 (14.3)	10 (13.2)	6 (7.5)
Cough	5 (8.2)	8 (14.3)	15 (19.7)	5 (6.3)
Dyspnea	10 (16.4)	5 (8.9)	8 (10.5)	8 (10.0)
Headache	10 (16.4)	4 (7.1)	11 (14.5)	6 (7.5)
Vomiting	10 (16.4)	4 (7.1)	9 (11.8)	6 (7.5)
Serious adverse event(s) [†]	14 (23.0)	21 (37.5)	23 (30.3)	23 (28.8)
Fatal adverse event(s)	7 (11.5)	7 (12.5)	5 (6.6)	6 (7.5)

Definition of abbreviation: RHD = right heart dysfunction.

Data are n (%) of patients.

*Adverse events reported in >15% of patients in any of the four subgroups shown by Medical Dictionary for Regulatory Activities preferred term.

[†]An event that resulted in death was immediately life threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalization, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.

reducing FVC decline than nintedanib alone in both subgroups. The mechanisms underpinning a slowing of lung function decline in patients with IPF treated with sildenafil remain to be elucidated, but it is apparent that the biological processes associated with fibrosis and vascular remodeling are interrelated (14). It has been hypothesized that apoptosis-resistant endothelial cells from remodeled pulmonary vessels can perpetuate fibrosis through the release of growth factors, such as TGF- β 1 (transforming growth factor β 1), vascular endothelial growth factor, endothelin-1, and bone morphogenetic proteins (15, 16). Given that phosphodiesterase-5 is expressed in the pulmonary vasculature, and increased in the pulmonary arteries of patients with IPF (17), it can be speculated that, by reducing endothelial cell apoptosis and pulmonary artery muscularization, sildenafil reduces the fibrogenic signals originating from pulmonary vessels. Studies in human lung fibroblasts have shown that, in the presence of a guanylyl cyclase activator, sildenafil inhibited TGF- β -induced fibroblast-to-myofibroblast differentiation (18). In skin fibroblasts from patients with systemic sclerosis, sildenafil significantly decreased the expression of several profibrotic factors that were upregulated by TGF- β 1 (19), whereas, in cardiac fibroblasts, sildenafil blocked TGF- β 1-induced fibroblast transformation and proliferation and the synthesis of collagen (20). Sildenafil has

also been shown to attenuate the progression of bleomycin-induced pulmonary fibrosis in animal models (21, 22).

In the overall trial population, nintedanib plus sildenafil was associated with stabilization of BNP compared with nintedanib alone (13). These new analyses have shown that the benefit of nintedanib plus sildenafil versus nintedanib alone on BNP levels was significantly greater in patients with echocardiographic signs of RHD at baseline (who had a much higher level of BNP at baseline), and, in patients with BNP levels above the median value at baseline. BNP is released into the circulation in response to ventricular dilatation or pressure overload (23) and is considered a marker of right ventricular dysfunction and pulmonary arterial hypertension (24). Elevated BNP has been associated with mortality in patients with IPF and other forms of ILD (25–27). It may be hypothesized that sildenafil reduces BNP in patients with IPF and advanced gas exchange impairment through its effects on pulmonary vascular remodeling and vasodilatation, and that this effect is more pronounced in patients who have greater right ventricular stress and so higher levels of BNP. A previous study of 15 patients with pulmonary hypertension and ILD found that treatment with sildenafil for 6 months resulted in a reduction in BNP levels (28). This suggests that patients with IPF who have raised BNP levels may be

more likely to benefit from a combination of nintedanib and sildenafil, but more data, including on long-term outcomes, would be needed to establish this.

The adverse event profiles of nintedanib plus sildenafil and nintedanib alone in both subgroups by signs of RHD were consistent with those observed in the overall trial population (13), and as expected, based on the known adverse event profiles of these drugs in patients with IPF (8, 9, 11).

Strengths of our analyses include that all patients were required to have an echocardiogram before randomization and the relatively large size of the subgroups with and without echocardiographic signs of RHD at baseline ($n = 117$ and $n = 156$). Our analyses also have some limitations. Signs of RHD were determined according to investigator judgement and were not confirmed by catheterization. The lack of a true placebo group prevents firm conclusions being drawn on the effects of nintedanib and sildenafil in patients with IPF and signs of RHD. The relatively short duration of the trial means that the long-term effects of nintedanib plus sildenafil in this patient population remain unknown; it is possible that, with longer duration of therapy, a greater benefit may have been seen. Similarly, the relatively small sample size does not exclude that the study was underpowered. Our analyses were not adjusted for multiplicity. The influence of

concomitant emphysema, which may contribute to vasculopathy, on changes in BNP has not yet been investigated. Although our study, as well as STEP-IPF (12), has provided data on the efficacy and safety of sildenafil in patients with IPF and severely impaired gas exchange who were at high risk of pulmonary hypertension based on echocardiography, these studies did not establish the benefits of sildenafil in patients with pulmonary hypertension confirmed by right heart catheterization. Future trial designs should balance the feasibility,

benefits, and risks of conducting right heart catheterization versus echocardiography in addressing the question of whether patients with IPF and pulmonary hypertension benefit from receiving sildenafil in addition to antifibrotic therapy. In conclusion, subgroup analyses of data from the INSTAGE trial demonstrated that the effect of nintedanib plus sildenafil versus nintedanib alone on changes in SGRQ total score and FVC were not significantly different between patients with or without echocardiographic signs of RHD at

baseline. The benefit of nintedanib plus sildenafil versus nintedanib alone on stabilizing BNP levels was more pronounced in patients with than in those without echocardiographic signs of RHD. ■

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