Effects of nintedanib on symptoms in patients with progressive pulmonary fibrosis

Marlies Wijsenbeek[1], Jeffrey J. Swigris[2], Yoshikazu Inoue[3], Michael Kreuter[4,5], Toby M. Maher[6,7], Takafumi Suda[8], Michael Baldwin[9], Heiko Mueller[10], Klaus B. Rohr[9] and Kevin R. Flaherty[11] on behalf of the INBUILD Trial Investigators

[1]Centre for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands. [2]National Jewish Health, Denver, CO, USA. [3]National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan. [4]Center for Pulmonary Medicine, Department of Pneumology, Mainz University Medical Center, Mainz, Germany. [5]Pulmonary, Critical Care and Sleep Medicine, Marienhaus Clinic Mainz, Mainz, Germany. [6]Inflammation, Repair and Development Section, National Heart and Lung Institute, Imperial College London, London, UK. [7]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. [8]Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan. [9]Boehringer Ingelheim International GmbH, Ingelheim, Germany. [10]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany. [11]Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA.

Corresponding author: Marlies Wijsenbeek (m.wijsenbeek-lourens@erasmusmc.nl)

Shareable abstract (@ERSpublications)
Based on changes in scores on the Living with Pulmonary Fibrosis (L-PF) questionnaire, nintedanib reduced worsening of dyspnoea, fatigue and cough over 52 weeks in patients with progressive pulmonary fibrosis https://bit.ly/3t7k4Im

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Abstract

Background Dyspnoea and cough can have a profound impact on the lives of patients with pulmonary fibrosis. We investigated the effects of nintedanib on the symptoms and impact of pulmonary fibrosis in patients with progressive pulmonary fibrosis (PPF) in the INBUILD trial using the Living with Pulmonary Fibrosis (L-PF) questionnaire.

Methods Patients had a fibrosing interstitial lung disease (ILD) (other than idiopathic pulmonary fibrosis) of >10% extent on high-resolution computed tomography (HRCT) and met criteria for ILD progression within the prior 24 months. Patients were randomised 1:1 to receive nintedanib or placebo. Changes in L-PF questionnaire scores from baseline to week 52 were assessed using mixed models for repeated measures.

Results In total, 663 patients were treated. Compared with placebo, there were significantly smaller increases (worsenings) in adjusted mean L-PF questionnaire total (0.5 *versus* 5.1), symptoms (1.3 *versus* 5.3), dyspnoea (4.3 *versus* 7.8) and fatigue (0.7 *versus* 4.0) scores in the nintedanib group at week 52. L-PF questionnaire cough score decreased in the nintedanib group and increased in the placebo group (−1.8 *versus* 4.3). L-PF questionnaire impacts score decreased slightly in the nintedanib group and increased in the placebo group (−0.2 *versus* 4.6). Similar findings were observed in patients with a usual interstitial pneumonia-like fibrotic pattern on HRCT and in patients with other fibrotic patterns on HRCT.

Conclusion Based on changes in L-PF questionnaire scores, nintedanib reduced worsening of dyspnoea, fatigue and cough and the impacts of ILD over 52 weeks in patients with PPF.

Introduction

Symptoms of dyspnoea and cough, as well as fatigue, can have a profound impact on the lives of patients with pulmonary fibrosis [1–3]. Current approaches to the management of pulmonary fibrosis aim to slow disease progression, minimise symptoms and preserve patients' health-related quality of life (HRQoL). Reliable, valid and responsive patient-reported outcomes are needed to evaluate the impact of disease on patients' lives and the effects of interventions [4, 5]. The Living with Pulmonary Fibrosis (L-PF) questionnaire was developed to evaluate symptoms and their impacts in patients with idiopathic pulmonary fibrosis (IPF) and other forms of progressive fibrosing interstitial lung disease (ILD) (referred to as progressive pulmonary fibrosis (PPF)) and has been shown to include items relevant to these patients [3, 6, 7].

In the INBUILD trial of nintedanib in patients with PPF, nintedanib reduced the rate of decline in forced vital capacity (FVC) compared with placebo [8, 9]. Absolute changes in L-PF questionnaire cough and dyspnoea domain scores at week 52 were defined as secondary end-points [8]. These scores were shown to be responsive to changes in disease severity and perceptions of health [10]. In addition, meaningful within-patient change thresholds for deterioration in these scores were ascertained, which can be used to interpret the effect of interventions [10]. We investigated the effects of nintedanib on the symptoms and impact of pulmonary fibrosis based on changes in L-PF questionnaire scores in the INBUILD trial.

Materials and methods

Patients

The design of the INBUILD trial has been published and the protocol is publicly available [8]. Briefly, patients had an ILD other than IPF, an extent of fibrosis on high-resolution computed tomography (HRCT) >10%, FVC ⩾45% predicted and diffusing capacity of the lung for carbon monoxide (D_{LCO}) ⩾30– <80% predicted. Patients met one of the following criteria for ILD progression within the prior 24 months despite management deemed appropriate in clinical practice: relative decline in FVC ⩾10% predicted; relative decline in FVC ⩾5– <10% predicted and worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; worsened respiratory symptoms and increased extent of fibrosis on HRCT.

Trial design

Patients were randomised 1:1 to receive nintedanib 150 mg twice daily or placebo, stratified by fibrotic pattern on HRCT (usual interstitial pneumonia (UIP)-like fibrotic pattern or other fibrotic patterns) (defined in Flaherty *et al.* [8]). Patients who discontinued treatment were asked to attend all further visits as originally planned. The primary end-point (annual rate of decline in FVC in mL per year) was assessed over 52 weeks.

The trial was carried out in compliance with the protocol, the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation, and was approved by local authorities. All patients provided written informed consent before study entry.

Methods

The L-PF questionnaire is accessible *via*: https://eprovide.mapi-trust.org/instruments/living-with-pulmonary-fibrosis-l-pf-impacts-questionnaire and https://eprovide.mapi-trust.org/instruments/living-with-pulmonary-fibrosis-l-pf-symptoms-questionnaire. In summary, this questionnaire comprises 44 items, each rated on a 5-point scale (0–4). It includes a symptoms module (23 items) and an impacts module (21 items). Recall for items in the symptoms module is the past 24 h. Recall for items in the impacts module is the past week. The symptoms module has three domains: dyspnoea, cough and fatigue. The total score and scores on the symptoms module, impacts module, and dyspnoea, cough and fatigue domains range from 0 to 100, with higher scores indicating greater impairment. In the INBUILD trial, the L-PF questionnaire was completed at baseline and at weeks 12, 24, 36 and 52.

Analyses

Absolute changes in L-PF questionnaire total, impacts (module), symptoms (module), dyspnoea (domain), cough (domain) and fatigue (domain) scores at week 52 were assessed in the overall population using mixed models for repeated measures, with fixed effects for baseline score, fibrotic pattern on HRCT (UIP-like fibrotic pattern or other fibrotic patterns), visit, treatment-by-visit interaction, baseline-by-visit interaction and random effect for patient. Within-patient errors were modelled using an unstructured variance-covariance structure. Changes in these scores were also assessed in subgroups of patients with a UIP-like fibrotic pattern on HRCT and in patients with other fibrotic patterns on HRCT, and in subgroups by ILD diagnosis (hypersensitivity pneumonitis, idiopathic non-specific interstitial pneumonia (NSIP), unclassifiable idiopathic interstitial pneumonia (IIP), autoimmune disease-related ILDs and other ILDs). In these subgroup analyses, treatment-by-subgroup interaction and treatment-by-visit-by-subgroup interaction were included instead of the treatment-by-visit interaction. Interaction p-values were calculated to assess potential heterogeneity in the effect of nintedanib *versus* placebo across the subgroups.

Changes in the dyspnoea, cough and fatigue domain scores and the impacts score were assessed in subgroups based on tertiles of these scores at baseline (*i.e.* <10.3, ⩾10.3– <26.4 and ⩾26.4 points for dyspnoea; <25, ⩾25– <50 and ⩾50 points for cough; <30, ⩾30– <50, ⩾50 points for fatigue; <32.8, ⩾32.8– <54.9 and ⩾54.9 points for impacts). In these subgroup analyses, the fixed effects for baseline and baseline-by-visit were excluded. Meaningful change thresholds in the dyspnoea score (6 or 7 points) and cough score (4 or 5 points) were used to differentiate patients who were stable or improved from those who

deteriorated at week 52, as defined in a previous analysis of data from the INBUILD trial [10]. Respective odds ratios and confidence intervals were assessed using a logistic regression model, with the terms treatment, baseline value of the end-point as a continuous covariate and HRCT pattern as a binary covariate. Missing data at week 52 were imputed using a multiple imputation approach.

Analyses were conducted in patients who received at least one dose of trial drug. Changes from baseline in L-PF questionnaire scores in the overall population and in patients with a UIP-like fibrotic pattern on HRCT were pre-specified in the protocol. The other analyses were conducted *post hoc*. No adjustment was made for multiple testing and p-values are considered nominal.

Results

Patients

In total, 663 patients received the trial drug (332 nintedanib, 331 placebo). Their baseline characteristics have been published [8]. Briefly, patients had a mean age of 65.8 years, 53.7% were male and 62.1% had a UIP-like fibrotic pattern on HRCT. Mean FVC was 69.0% predicted. The ILD diagnoses were hypersensitivity pneumonitis (26.1%), autoimmune disease-related ILDs (25.6%), idiopathic NSIP (18.9%), unclassifiable IIP (17.2%) and other ILDs (12.2%). Comorbidities present at baseline are summarised in supplementary table S1. Medications taken at baseline are summarised in supplementary table S2. Baseline FVC and D_{LCO} % predicted in subgroups by fibrotic pattern on HRCT and by ILD diagnosis are shown in supplementary table S3.

L-PF questionnaire scores at baseline

At baseline, mean L-PF questionnaire total, symptoms, impacts, cough and fatigue scores were similar in patients with a UIP-like fibrotic pattern on HRCT and in patients with other fibrotic patterns on HRCT, but mean dyspnoea score was higher (worse) in patients with other fibrotic patterns than in patients with a UIP-like fibrotic pattern (table 1). L-PF questionnaire scores showed some variability across the subgroups by ILD diagnosis, particularly in the cough score (supplementary table S4).

Changes in L-PF questionnaire scores at week 52

In the placebo group, adjusted mean L-PF questionnaire scores increased (worsened) from baseline to week 52 (figure 1a). There were significantly smaller increases in adjusted mean total, symptoms, dyspnoea and fatigue scores in the nintedanib group than in the placebo group, while in the nintedanib group, the cough score decreased (improved) and there was almost no change in the impacts score (figure 1a). Similar findings were observed in patients with a UIP-like fibrotic pattern on HRCT (figure 1b) and in patients with other fibrotic patterns on HRCT (figure 1c).

In the placebo group, patients with autoimmune disease-related ILDs had numerically smaller changes in L-PF questionnaire scores than patients with other diagnoses, although there was less of a difference between patients with autoimmune disease-related ILDs and patients with other diagnoses in change in dyspnoea score (figure 2 and supplementary figures S1–S5). The effects of nintedanib on changes in L-PF questionnaire scores were numerically smaller in patients with autoimmune disease-related ILDs than in the other diagnostic subgroups; however, the interaction p-values did not indicate heterogeneity in the effect of nintedanib among these subgroups (p>0.05 for all).

TABLE 1 Living with Pulmonary Fibrosis questionnaire scores at baseline in the overall population and in subgroups by high-resolution computed tomography (HRCT) pattern

	Overall population				UIP-like fibrotic pattern on HRCT				Other fibrotic patterns on HRCT			
	Nintedanib		Placebo		Nintedanib		Placebo		Nintedanib		Placebo	
	Patients	Score	Patients	Score	Patients	Score	Patients	Score	Patients	Score	Patients	Score
Total	329	39.0±19.3	321	39.0±18.6	204	37.7±18.9	201	37.4±17.8	125	41.1±19.8	120	41.8±19.8
Impacts	332	44.8±22.5	328	44.4±21.7	206	43.6±22.3	205	42.3±20.9	126	46.7±22.8	123	47.8±22.6
Symptoms	329	33.2±17.9	323	34.0±17.3	204	31.8±17.3	201	32.5±16.5	125	35.6±18.7	122	36.4±18.4
Dyspnoea	329	22.1±17.9	323	21.2±18.1	204	20.3±16.5	201	18.6±16.2	125	25.1±19.6	122	25.4±20.1
Cough	327	38.9±26.4	320	40.0±26.5	203	38.1±26.1	199	38.6±26.4	124	40.3±27.1	121	42.2±26.6
Fatigue	328	38.8±20.4	323	40.9±19.6	203	37.1±19.6	201	40.3±19.8	125	41.6±21.4	122	41.9±19.4

Data are presented as n or mean±SD. Not all patients provided data for all variables. UIP: usual interstitial pneumonia.

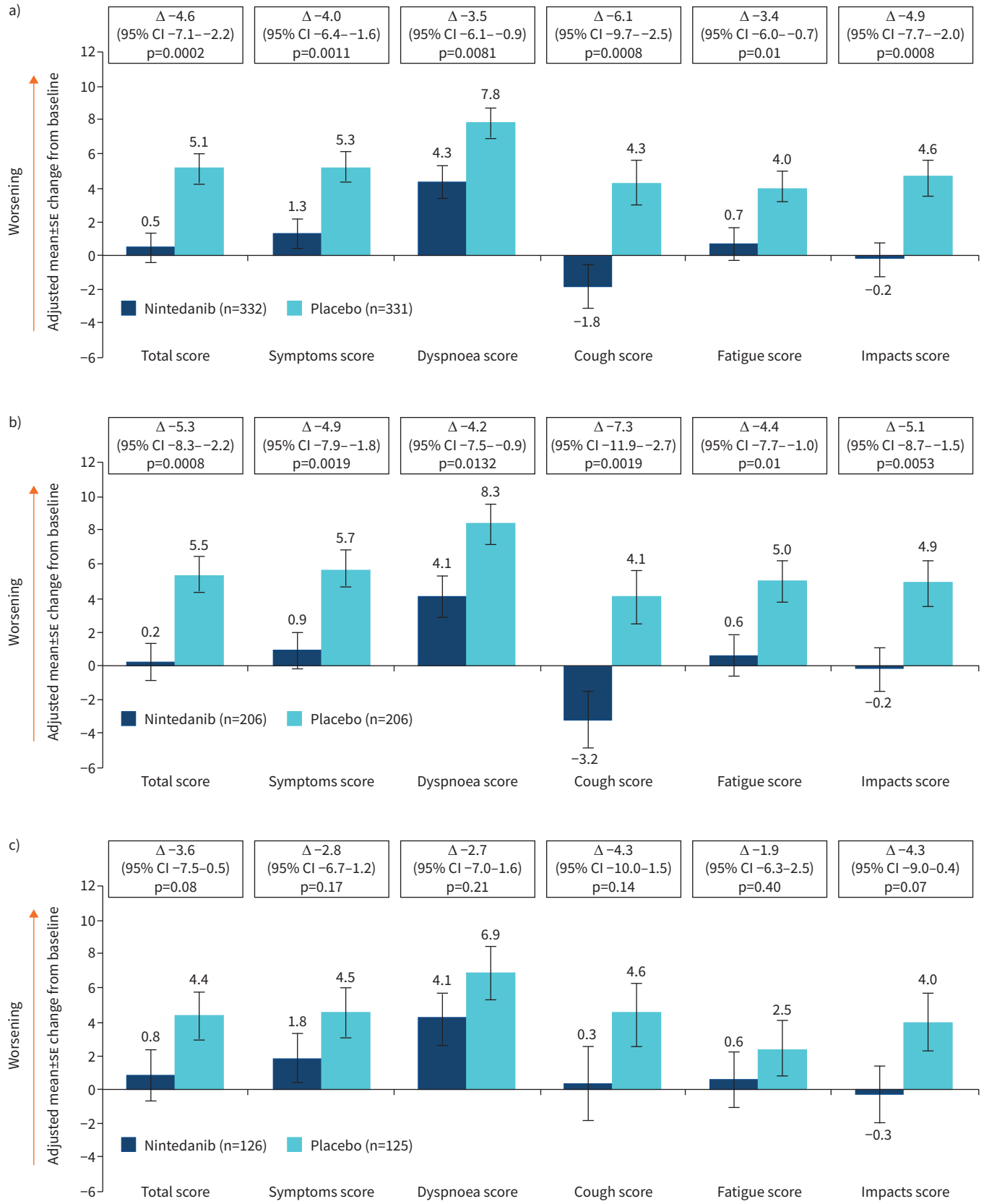

FIGURE 1 Changes in Living with Pulmonary Fibrosis questionnaire scores at week 52 in a) the overall population, b) patients with a usual interstitial pneumonia-like fibrotic pattern on high-resolution computed tomography (HRCT) and c) patients with other fibrotic patterns on HRCT.

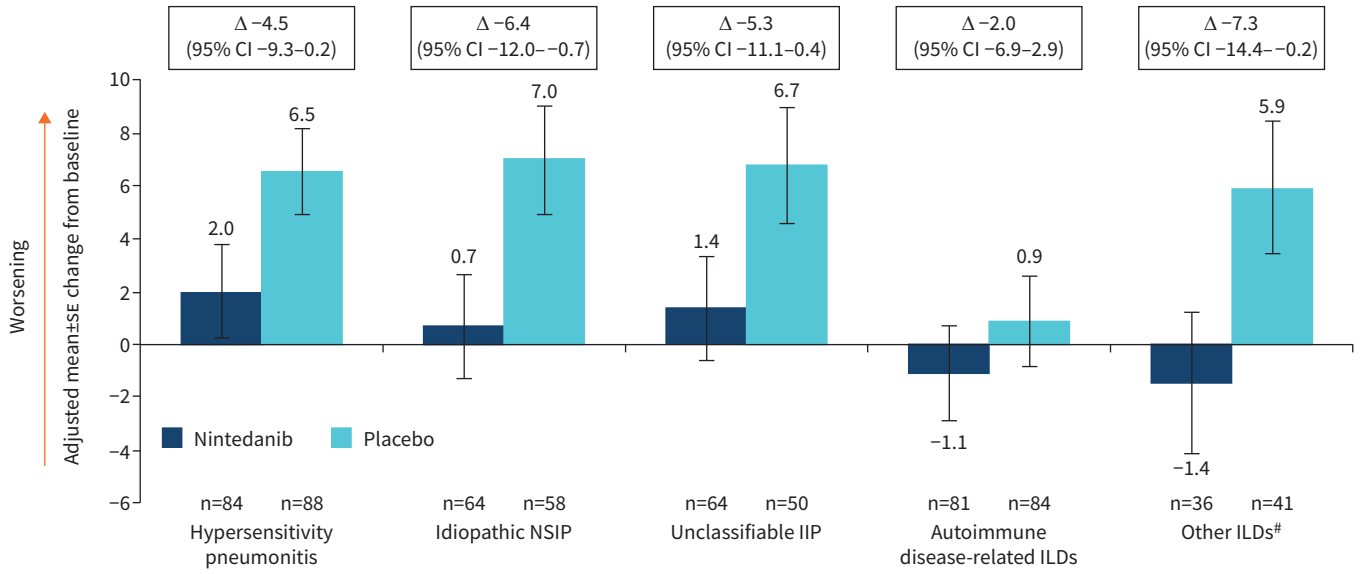

FIGURE 2 Changes in Living with Pulmonary Fibrosis questionnaire total score at week 52 by interstitial lung disease (ILD) diagnosis. #: other ILDs included sarcoidosis, exposure-related ILDs and other terms in the "Other fibrosing ILDs" category of the case report form. IIP: idiopathic interstitial pneumonia; NSIP: non-specific interstitial pneumonia. Treatment-by-visit-by-subgroup interaction p=0.71.

Changes in L-PF questionnaire scores at week 52 in subgroups by baseline score

In both the placebo and nintedanib groups, there was no clear pattern in change in dyspnoea score from baseline to week 52 among the subgroups based on tertiles of baseline score (supplementary figure S6). The increase (worsening) in dyspnoea score was smaller in the nintedanib group than in the placebo group across the subgroups; the effect of nintedanib was numerically lowest in patients with scores in the lowest (best) tertile at baseline.

Cough scores increased (worsened) from baseline to week 52 in patients with scores in the lowest (best) two tertiles at baseline, with numerically smaller increases in the nintedanib group than in the placebo group (supplementary figure S7). In both treatment groups, cough scores decreased (improved) from baseline to week 52 in patients with scores in the highest (worst) tertile at baseline.

Fatigue scores increased (worsened) from baseline to week 52 in patients with scores in the lowest (best) tertile at baseline, with a numerically smaller increase in the nintedanib group than in the placebo group (supplementary figure S8). Fatigue scores decreased (improved) in patients with scores in the highest (worst) tertile at baseline, with a numerically larger decrease in the nintedanib group than in the placebo group (supplementary figure S8).

Impacts scores increased (worsened) from baseline to week 52 in patients with scores in the lowest (best) two tertiles at baseline, with numerically smaller increases in the nintedanib group than in the placebo group (supplementary figure S9). Impacts scores decreased (improved) from baseline to week 52 in patients in the highest (worst) tertile at baseline, with a numerically larger decrease in the nintedanib group (supplementary figure S9).

Interaction p-values did not indicate heterogeneity among subgroups by baseline score in the effect of nintedanib on changes in dyspnoea score (p=0.45), cough score (p=0.35), fatigue score (p=0.82) or impacts score (p=0.41).

Meaningful change thresholds to differentiate patients who were stable or improved from those who deteriorated in L-PF questionnaire dyspnoea and cough scores at week 52

A smaller proportion of patients who received nintedanib than placebo had a deterioration in dyspnoea score that met meaningful change thresholds (OR 0.67 (95% CI 0.48–0.94) and 0.70 (95% CI 0.50–0.98) for increases of ⩾6 and ⩾7 points, respectively) (table 2). A smaller proportion of patients who received nintedanib than placebo had a deterioration in cough score that met meaningful change thresholds (OR 0.65 (95% CI 0.46–0.92) and 0.57 (95% CI 0.40–0.81) for increases of ⩾4 and ⩾5 points, respectively) (table 3).

TABLE 2 Proportion of patients who met thresholds to differentiate patients who were stable or improved from those who deteriorated in Living with Pulmonary Fibrosis questionnaire dyspnoea domain score at week 52

	Nintedanib (n=329)	Placebo (n=323)	OR (95% CI)
Threshold of ⩾6 points			
Increase in score ⩾6 points (worsening)	121 (36.8)	150 (46.4)	0.67 (0.48–0.94)
No increase in score ⩾6 points (stability or improvement)	208 (63.2)	173 (53.6)	1.48 (1.06–2.07)
Threshold of ⩾7 points			
Increase in score ⩾7 points (worsening)	114 (34.7)	139 (43.0)	0.70 (0.50–0.98)
No increase in score ⩾7 points (stability or improvement)	215 (65.3)	184 (57.0)	1.43 (1.02–2.00)

Data are presented as n (%), unless otherwise stated. Missing data at week 52 were imputed using a multiple imputation approach. Pooled results following multiple imputation are shown, with the n rounded to a digit.

Discussion

Changes in L-PF questionnaire scores over 52 weeks suggested that, in patients with PPF, nintedanib slowed the worsening of dyspnoea, fatigue and cough and the impacts of the disease on patients' lives. Based on meaningful change thresholds for the dyspnoea and cough scores, which were estimated using data from this patient population [10], smaller proportions of patients treated with nintedanib than placebo had clinically meaningful worsening of dyspnoea and cough over 52 weeks. This is the first trial in which changes in patient-reported outcomes over 52 weeks have suggested a benefit of antifibrotic therapy on symptoms and impact of disease in the overall population of an individual trial.

Although the mechanisms behind the observed effects of nintedanib on worsening of cough and dyspnoea are unknown, analyses of data from the INPULSIS trials in patients with IPF and the SENSCIS trial in patients with systemic sclerosis-associated ILD [11, 12], as well as data from observational studies in patients with IPF [13, 14], have shown that patients with the greatest declines in FVC have the greatest declines in patient-reported outcomes. Several studies have demonstrated moderate to strong correlations between FVC and patient-reported outcomes at baseline [12, 15–17], although other studies have demonstrated weaker correlations [18–20]. Taken together, these data suggest that although patient-reported outcomes assess different dimensions of disease than lung function, preserving lung function may be beneficial in preventing deterioration in symptoms and HRQoL in patients with PPF.

In clinical trials, several tools have been used to measure the effects of antifibrotic therapies on HRQoL in patients with fibrosing ILDs, but individual trials have shown only small changes in patient-reported outcomes in the active treatment and placebo groups, with no significant difference between the groups [8, 21–27]. A previous analysis of data collected using the King's Brief Interstitial Lung Disease (K-BILD) questionnaire found no significant difference in change in symptoms in patients treated with nintedanib *versus* placebo in the INBUILD trial [8]. This may partly be related to the questionnaires used. The L-PF questionnaire is a relatively new questionnaire developed specifically for patients with pulmonary fibrosis. While more research is needed, in a recent appraisal of nine patient-reported outcome measures by patients, clinicians, regulatory advisors and payer advisors, the L-PF questionnaire was considered to best capture the severity, frequency or interference with daily life of the symptoms (shortness of breath on exertion, cough and fatigue) and impacts of disease (on physical functioning, activities of daily living and emotions) that are most important to patients with pulmonary fibrosis [3].

TABLE 3 Proportion of patients who met thresholds to differentiate patients who were stable or improved from those who deteriorated in Living with Pulmonary Fibrosis questionnaire cough domain score at week 52

	Nintedanib (n=327)	Placebo (n=320)	OR (95% CI)
Threshold of ⩾4 points			
Increase in score ⩾4 points (worsening)	136 (41.6)	162 (50.6)	0.65 (0.46–0.92)
No increase in score ⩾4 points (stability or improvement)	191 (58.4)	158 (49.4)	1.54 (1.08–2.18)
Threshold of ⩾5 points			
Increase in score ⩾5 points (worsening)	113 (34.6)	148 (46.3)	0.57 (0.40–0.81)
No increase in score ⩾5 points (stability or improvement)	214 (65.4)	172 (53.8)	1.77 (1.24–2.53)

Data are presented as n (%), unless otherwise stated. Missing data at week 52 were imputed using a multiple imputation approach. Pooled results following multiple imputation are shown, with the n rounded to a digit.

The INBUILD trial enrolled a broad range of patients with PPF. We observed that changes in L-PF questionnaire scores in the placebo group, and differences between scores in the nintedanib and placebo groups, were smaller in patients with autoimmune disease-related ILDs than in those with other diagnoses. While the reasons for this are unclear, it may be that the greater impacts of extrapulmonary manifestations of disease on symptoms and HRQoL in patients with autoimmune disease-related ILDs alter these patients' perceptions of the symptoms or impacts of pulmonary fibrosis. Further research is needed into how extrapulmonary manifestations of systemic disease may alter the perception of lung-specific symptoms and the overall impact of ILD.

In our analyses, the effects of nintedanib were not limited to patients with a particularly high or low symptom burden at baseline. For all scores except the dyspnoea score, there was a trend that the subgroup with the worst symptom score at baseline showed the greatest improvement in score over 52 weeks, irrespective of treatment, while the subgroup with the best symptom score at baseline showed the greatest worsening. A possible explanation for this is regression to the mean. Further analyses of data from the INBUILD trial will investigate the relationship between L-PF questionnaire scores at baseline, changes in these scores and progression of PPF.

Strengths of the current analyses include the robust collection of data in the setting of a clinical trial, the large sample size and the relevant items and short recall period used in the L-PF questionnaire. Limitations include the *post hoc* nature of some of the analyses and the small number of patients in the subgroups by ILD diagnosis; numerical differences between these subgroups should be interpreted with caution. The meaningful change thresholds for deterioration in L-PF questionnaire dyspnoea and cough scores need validation in other cohorts. While these data are encouraging, research in other cohorts is needed into the impact of nintedanib on dyspnoea, cough and fatigue in patients with pulmonary fibrosis. The effects of nintedanib on gastrointestinal side-effects and on "overall" HRQoL were not assessed using the L-PF questionnaire.

In conclusion, in patients with PPF, changes in L-PF questionnaire scores suggest that nintedanib reduces worsening of dyspnoea, fatigue and cough and the impacts of disease over 52 weeks. Further studies in different patient populations are needed to extend these findings.

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This clinical trial was prospectively registered at ClinicalTrials.gov with identifier number NCT02999178. To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use https://vivli.org to request access to study data and visit www.mystudywindow.com/msw/datasharing for further information.

Ethics statement: The trial was carried out in compliance with the protocol, the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation, and was approved by local authorities. All patients provided written informed consent before study entry.

A video abstract summarising the results of this study is available at: www.globalmedcomms.com/respiratory/wijsenbeek/nintedanib_L-PF

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