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Original article

The effect of nintedanib on health-related quality of life in Japanese patients with progressive fibrosing interstitial lung diseases: A subset analysis of the INBUILD trial

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ABSTRACT

Background: In previous Japanese subgroup/subset analyses of the global INBUILD trial, nintedanib reduced the annual rate of forced vital capacity (FVC) decline and the risk of disease progression in patients with progressive fibrosing interstitial lung diseases (PF-ILDs). This exploratory subset analysis assessed the effect of nintedanib on symptoms and impacts of pulmonary fibrosis in Japanese patients with PF-ILDs, including those with usual interstitial pneumonia (UIP)-like fibrotic pattern on high-resolution computed tomography (HRCT).

Methods: This analysis included Japanese patients who received at least one dose of study treatment in the randomized, double-blind, placebo-controlled INBUILD trial. The Living with Pulmonary Fibrosis (L-PF) questionnaire was used to assess pulmonary fibrosis symptoms and impacts (higher scores indicated greater impairment) at baseline and weeks 12–52.

Results: In total, 108 Japanese patients (nintedanib: n = 52; placebo: n = 56) were included; 84 patients had UIP-like fibrotic pattern on HRCT. In the total Japanese subgroup and in those with UIP-like fibrotic pattern, numerically greater increases in L-PF total, symptoms total, symptoms fatigue domain, and impacts scores were observed in the placebo group than in the nintedanib group at all timepoints, starting from week 12. A numerically greater increase in the symptoms dyspnea domain score was observed with placebo versus nintedanib starting from week 36. Throughout the study, the symptoms cough domain score increased in the placebo group but decreased in the nintedanib group.

Conclusions: Our findings demonstrate that nintedanib has the potential to reduce the worsening of symptoms and impacts of pulmonary fibrosis in Japanese patients with PF-ILDs.

1. Introduction

Interstitial lung disease (ILD) describes a diverse group of over 200 mostly rare diffuse parenchymal lung diseases [1,2]. Some patients with ILDs develop a progressive phenotype, known as progressive fibrosing ILD (PF-ILD) or progressive pulmonary fibrosis (PPF), despite receiving appropriate disease management [1–3]. PF-ILDs are characterized by symptoms, such as dyspnea, cough, and fatigue, that greatly reduce the health-related quality of life (HRQoL) of the affected individuals [4,5].

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Therefore, measuring the effect of PF-ILD on HRQoL is crucial for evaluating treatment efficacy from the perspective of patients, as well as other key stakeholders, including clinicians, payers, and regulators [5]. As such, validated questionnaires are important to monitor changes in symptoms and the associated impacts in patients with PF-ILD, and questionnaires tailored to this specific condition are needed.

Abbreviations

CI	confidence interval
DL_{CO}	diffusing capacity of the lung for carbon monoxide
FVC	forced vital capacity
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
L-PF	Living with Pulmonary Fibrosis
MMRM	mixed model for repeated measures
OR	odds ratio
PF-ILD	progressive fibrosing interstitial lung disease
PPF	progressive pulmonary fibrosis
SSc-ILD	systemic sclerosis-associated interstitial lung disease
UIP	usual interstitial pneumonia

Nintedanib is a small-molecule intracellular inhibitor of multiple tyrosine kinases that are involved in the initiation and progression of lung fibrosis [6]. Nintedanib has been approved for the treatment of patients with idiopathic pulmonary fibrosis (IPF), PF-ILDs other than IPF, and systemic sclerosis-associated ILD (SSc-ILD) in Europe [7,8], the United States [9], and Japan [10].

In the global, randomized, double-blind, phase 3 INBUILD trial in patients with PF-ILDs other than IPF, nintedanib significantly reduced the annual rate of decline in forced vital capacity (FVC) over the initial 52-week study period compared with placebo [11], and reduced the risk of events indicating ILD progression over the whole trial [12]. Nintedanib also slowed the progression of dyspnea, fatigue, and cough, and reduced the impacts of pulmonary fibrosis on HRQoL, assessed using the Living with Pulmonary Fibrosis (L-PF) questionnaire [12,13]. These findings suggest that preserving lung function is key to preventing the deterioration of pulmonary fibrosis symptoms and the impacts of disease in patients with PF-ILDs.

Subgroup and subset analyses of Japanese patients in the INBUILD trial showed that nintedanib reduced the annual rate of decline in FVC and reduced the risk of ILD progression or death, as well as the risk of acute exacerbation or death [14,15]. These results demonstrated that the efficacy of nintedanib in Japanese patients was consistent with that reported in the overall INBUILD trial population [11,12,14,15].

In this analysis, we evaluated the effect of nintedanib on symptoms and the impacts of pulmonary fibrosis in Japanese patients with PF-ILDs using the Japanese version of the L-PF questionnaire to assess the consistency of the effects in this patient population compared with the overall trial population, and whether there were any racial and ethnic differences in these effects.

2. Patients and methods

2.1. Trial design

The design of the INBUILD trial (NCT02999178) has been described previously [11]. Briefly, INBUILD was a randomized, double-blind, placebo-controlled, parallel-group trial that enrolled patients at 153 sites located in 15 countries and was conducted between February 2017 and August 2019. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, local regulations, and the protocol, which was approved by the independent ethics committees between February 2017 and September 2017 (Supplementary Table 1). All patients provided written informed consent prior to enrolment. Patients were randomized to receive either oral nintedanib 150 mg twice daily or placebo at a 1:1 ratio, stratified by fibrotic pattern on HRCT (UIP fibrotic pattern or other fibrotic patterns). All patients, including those who discontinued the study treatment prematurely, were encouraged to attend all planned study visits, unless they withdrew consent for participation. The primary endpoint (annual rate of decline in FVC in mL/year) was assessed over 52 weeks. This was the first trial where the Japanese version of the L-PF questionnaire was used in patients with PF-ILD.

2.2. Patients

To be eligible for inclusion in the INBUILD trial, patients had to be ≥ 18 years old (≥20 years old in Japan), have a physician-diagnosed PF-ILD other than IPF, a disease extent of >10% lung volume on high-resolution computed tomography (HRCT; confirmed by central review), ILD progression within the 24 months before screening, an FVC of ≥45% of the predicted value, and a diffusing capacity of the lung for carbon monoxide (DL_{CO}; corrected for hemoglobin) of 30% to <80% of the predicted value [11]. ILD progression was defined as ≥1 of the following at any point within the 24 months before screening, despite appropriate clinical management with agents other than nintedanib and pirfenidone: relative FVC decline of ≥10% of the predicted value; relative FVC decline of 5% to <10% of the predicted value and worsening of respiratory symptoms, or increased extent of fibrosis on HRCT; worsening of respiratory symptoms and increased extent of fibrosis on HRCT. In the INBUILD trial, an enrichment design was planned, with stratification of the trial population so that two-thirds of the patients had a usual interstitial pneumonia (UIP)-like fibrotic pattern and one-third had other fibrotic patterns (i.e., a 2:1 ratio). The sample size (600 patients; 300 per treatment group) was calculated to provide adequate power to detect a clinically meaningful treatment difference in either of the co-primary populations, that is, the overall population and patients with a UIP-like fibrotic pattern [11,16]. Therefore, this analysis was conducted in all Japanese patients who received at least one dose of study treatment and in Japanese patients with a UIP-like fibrotic pattern (a pre-specified co-primary population in the INBUILD trial).

2.3. Endpoints and statistical analyses

The focus of the present exploratory subset analysis was the change in L-PF questionnaire score in Japanese participants of the INBUILD trial. L-PF is a modified version of the Living with Idiopathic Pulmonary Fibrosis questionnaire, which was developed specifically to assess symptoms and the impacts of disease in patients with pulmonary fibrosis [17,18]. The L-PF questionnaire consists of 44 items divided into two modules: symptoms (23 items) and impacts (21 items). The items in the symptoms module assess dyspnea, cough, and fatigue, with a recall period of 24 h. The items in the impacts module assess HRQoL with a recall period of 1 week. Responses for each item range from 0 (“not at all”) to 4 (“extremely”), and each L-PF module score ranges from 0 to 100, with higher scores indicating greater impairment [17]. A previous analysis of INBUILD showed the responsiveness of L-PF symptoms dyspnea and cough domain scores to changes in disease severity, with estimated meaningful change thresholds of 6–7 and 4–5 points, respectively [18]. In the INBUILD trial, patients completed the L-PF questionnaire at baseline and at weeks 12, 24, 36, and 52. The L-PF questionnaire was translated into Japanese and linguistically validated by the Mapi Research Trust (Lyon, France) using a rigorous translation process (Supplementary File 1) [19,20]. The English version of the L-PF

questionnaire has been published previously [11,13].

In the trial protocol, the secondary efficacy endpoints included absolute change in the L-PF symptoms dyspnea and cough domain scores from baseline to week 52. The absolute change in the L-PF total, symptoms total, symptoms fatigue domain, and impacts scores from baseline to week 52 were included among the further efficacy endpoints.

Among the Japanese patients who were evaluated, the changes in the L-PF total, symptoms total, dyspnea, cough, and fatigue domains, and impacts scores from baseline to week 52 were assessed using mixed models for repeated measures (MMRM), with fixed effects for baseline, HRCT pattern, treatment-by-visit interaction, and baseline-by-visit interaction. In Japanese patients with a UIP-like fibrotic pattern on HRCT, these outcomes were assessed using MMRM, with fixed effects for baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Within-patient errors were modelled using an unstructured variance–covariance structure. Adjusted means and 95% confidence intervals (CIs) were calculated based on the data for all patients in the model. Meaningful change thresholds (as previously described in the INBUILD study [18]) in the L-PF dyspnea score (≥6 or ≥7 points) and cough score (≥4 or ≥5 points) were used to differentiate between patients who were more likely to be stable or improved (i.e., with no absolute change in dyspnea or cough domain score) and those who had a greater likelihood of deterioration (i.e., absolute change in domain score). The odds ratios (ORs) and 95% CIs were calculated based on a logistic regression model; continuous covariates were treatment (nintedanib vs placebo) and baseline score for the endpoint, and the binary covariate was the HRCT pattern.

All analyses were prespecified, with the exception of the logistic regression analysis. SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA), was used for all analyses.

3. Results

3.1. Patients and L-PF questionnaire scores at baseline

A total of 108 Japanese patients with PF-ILD filled out the Japanese version of the L-PF questionnaire and were included in the present analysis, of whom 52 received nintedanib and 56 received placebo.

The baseline characteristics of the Japanese patients have been described previously [14]. The most common clinical ILD diagnoses were unclassifiable idiopathic interstitial pneumonia (n = 39; 36.1%), followed by hypersensitivity pneumonitis (n = 14; 13.0%) and non-specific interstitial pneumonia (n = 14; 13.0%). In total, 33 Japanese patients (30.6%) were diagnosed with autoimmune ILD.

At baseline, the mean L-PF scores were similar between two treatment arms and between the overall Japanese population and Japanese patients with a UIP-like fibrotic pattern. This similarity was also observed across the L-PF impacts and symptoms dyspnea, cough, and fatigue domain scores (Table 1).

3.2. Changes in L-PF questionnaire scores

In the overall Japanese population, greater increases in the adjusted mean change in the L-PF total, symptoms total, symptoms fatigue domain, and impacts scores were observed in the placebo group than in the nintedanib group from week 12 (Fig. 1A, B, E, F). The adjusted mean change in L-PF symptoms dyspnea domain score was higher with placebo than with nintedanib from week 36 (Fig. 1C). Throughout the study, the adjusted mean L-PF symptoms cough domain score increased in the placebo group and decreased in the nintedanib group (Fig. 1D).

At week 52, numerically greater increases in all L-PF scores were observed in the placebo group compared with the nintedanib group (Fig. 2). The adjusted mean change in the L-PF total score was 7.3 (95% CI: 3.9, 10.8) in the placebo group and 2.8 (95% CI: −0.7, 6.3) in the nintedanib group. Numerically greater increases with placebo versus nintedanib were observed in the adjusted mean symptoms total (7.8 [95% CI: 4.6, 10.9] vs 0.6 [95% CI: −2.6, 3.8]), symptoms dyspnea domain (9.0 [95% CI: 5.4, 12.5] vs 5.0 [95% CI: 1.4, 8.6]), symptoms fatigue domain (6.0 [95% CI: 2.1, 9.9] vs 0.5 [95% CI: −3.5, 4.5]), and impacts (6.9 [95% CI: 2.3, 11.4] vs 4.7 [95% CI: 0.1, 9.4]) scores. The adjusted mean symptoms cough domain score increased in the placebo group and decreased in the nintedanib group (8.5 [95% CI: 3.3, 13.6] vs −3.2 [95% CI: −8.5, 2.1]).

A similar pattern of change in L-PF scores was observed in Japanese patients with UIP-like fibrotic pattern on HRCT (Fig. 3). There were numerically greater adjusted mean changes in the placebo group versus the nintedanib group in the L-PF total, symptoms total, symptoms fatigue domain, and impacts scores from week 12 (Fig. 3A, B, E, F), and in the symptoms dyspnea domain score from week 36 (Fig. 3C). Throughout the study, the adjusted mean L-PF symptoms cough domain score increased in the placebo group and decreased in the nintedanib group (Fig. 3D).

At week 52, there were numerically greater increases in all L-PF scores with placebo versus nintedanib among Japanese patients with UIP-like fibrotic pattern on HRCT (Fig. 4). The adjusted mean change in the L-PF total score was 8.0 (95% CI: 4.3, 11.6) in the placebo group and 2.3 (95% CI: −1.6, 6.2) in the nintedanib group. Numerically greater increases with placebo versus nintedanib were observed in the adjusted mean symptoms total (8.7 [95% CI: 5.3, 12.2] vs 0.2 [95% CI: −3.6, 4.0]), symptoms fatigue domain (7.2 [95% CI: 3.0, 11.4] vs 0.5 [95% CI: −4.1, 5.0]), symptoms dyspnea domain (10.0 [95% CI: 6.1, 13.9] vs 4.8 [95% CI: 0.6, 9.1]), and impacts (7.3 [95% CI: 2.7, 11.9] vs 4.1 [95% CI: −0.9, 9.0]) scores. The adjusted mean symptoms cough domain score increased with placebo and decreased with nintedanib (9.7 [95% CI: 3.7, 15.7] vs −4.3 [95% CI: −10.8, 2.2]).

The number of patients with a deterioration in L-PF symptoms dyspnea domain score that met meaningful change thresholds was numerically lower in the nintedanib group than in the placebo group (OR: 0.57, 95% CI: 0.24, 1.34 for a change of ≥6 points, OR: 0.68, 95% CI: 0.29, 1.61 for ≥7 points; Table 2). The number of patients with a deterioration in L-PF symptoms cough domain score that met meaningful change thresholds was nominally significantly lower in the nintedanib group than in the placebo group (OR: 0.27, 95% CI: 0.11, 0.64 for a change of ≥4 points, OR: 0.23, 95% CI: 0.10, 0.56 for ≥5 points; Table 3).

Table 1
Baseline Living with Pulmonary Fibrosis (L-PF) questionnaire scores in Japanese patients.

Mean (SD) score	All Japanese patients			Japanese patients with UIP-like fibrotic pattern on HRCT		
	Nintedanib (n = 52)	Placebo (n = 56)	Total (n = 108)	Nintedanib (n = 39)	Placebo (n = 45)	Total (n = 84)
Total	30.5 (19.8)	29.0 (16.2)	29.7 (17.9)	30.2 (19.3)	30.5 (15.4)	30.4 (17.2)
Impacts	33.2 (22.2)	33.6 (19.7)	33.4 (20.8)	33.6 (21.0)	35.1 (18.2)	34.4 (19.5)
Symptoms total	27.8 (18.9)	24.3 (13.8)	26.0 (16.5)	26.8 (18.6)	26.0 (13.7)	26.4 (16.1)
Symptoms dyspnea domain	13.9 (14.9)	11.3 (12.0)	12.6 (13.5)	13.5 (14.2)	12.5 (12.8)	13.0 (13.4)
Symptoms cough domain	34.1 (29.3)	27.4 (22.7)	30.6 (26.2)	33.0 (30.0)	28.8 (22.9)	30.8 (26.3)
Symptoms fatigue domain	35.6 (21.4)	34.2 (19.3)	34.8 (20.2)	33.9 (20.4)	36.6 (19.0)	35.4 (19.6)

HRCT, high-resolution computed tomography; SD, standard deviation; UIP, usual interstitial pneumonia.

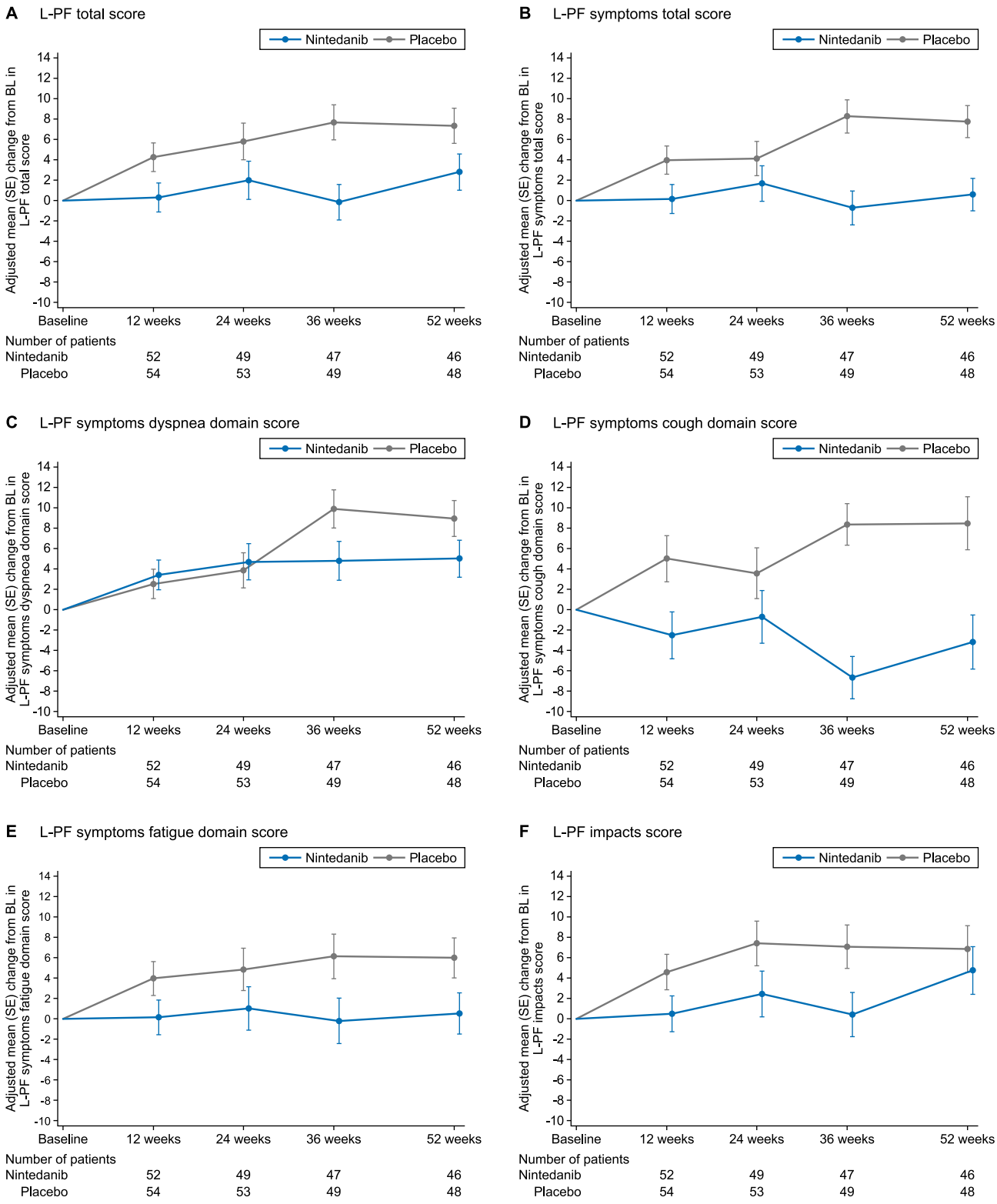

Fig. 1. Adjusted mean (standard error [SE]) change from baseline (BL) over 52 weeks in the Living with Pulmonary Fibrosis (L-PF) questionnaire (A) total, (B) symptoms total, (C) symptoms dyspnea domain, (D) symptoms cough domain, (E) symptoms fatigue domain, and (F) impacts scores in the overall Japanese population.

4. Discussion

In this subset analysis of the INBUILD trial in the overall Japanese population with PF-ILDs other than IPF and in Japanese patients with UIP-like fibrotic pattern on HRCT, nintedanib had positive effects on symptoms and impacts of pulmonary fibrosis across all L-PF scores. In the overall Japanese population, the L-PF questionnaire total score, the symptoms total and the individual symptom domains scores, and the impacts scores increased from baseline to week 52 in the placebo group, indicating a worsening of pulmonary fibrosis symptoms and patient

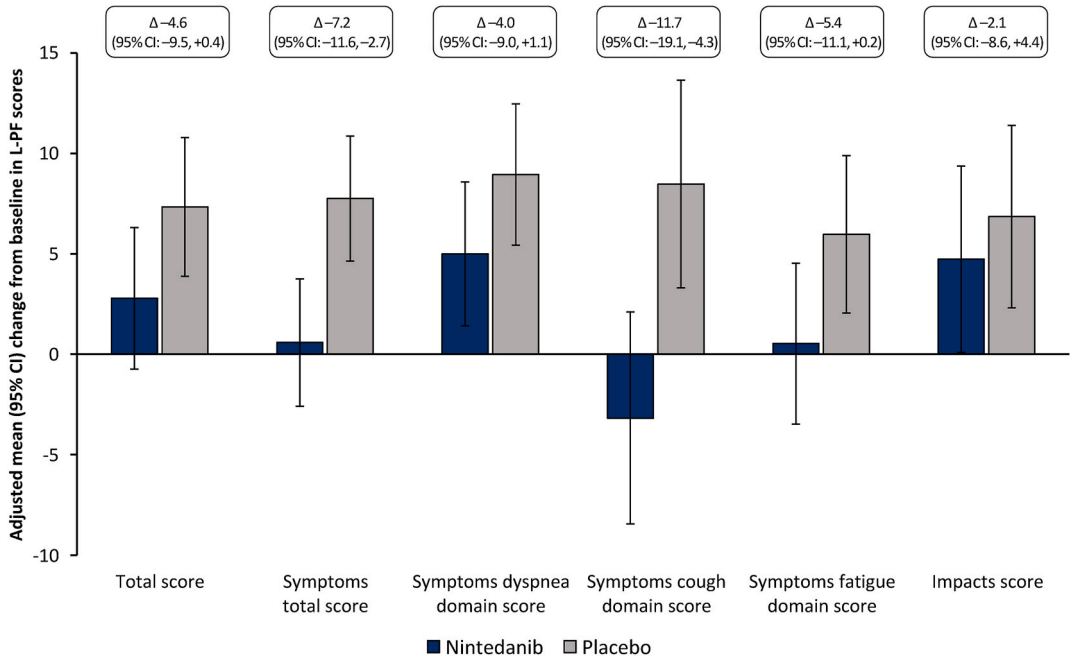

Fig. 2. Adjusted mean (95% confidence interval [CI]) change in the Living with Pulmonary Fibrosis (L-PF) questionnaire scores from baseline to week 52 in the overall Japanese population. For each score, the adjusted mean between-group difference (Δ) and 95% CI is presented above the graph.

HRQoL. In contrast, in the nintedanib group, the L-PF symptoms cough domain score numerically decreased, and numerically smaller increases versus placebo were observed in the L-PF total score, the symptoms total, dyspnea and fatigue domain scores, and impacts score, suggesting a lesser degree of worsening (or a greater degree of stabilization) with nintedanib. Similar improvements in pulmonary fibrosis symptoms and impacts scores were observed in Japanese patients with UIP-like fibrotic pattern on HRCT. These findings are similar to those observed in the overall population of the global INBUILD trial across all L-PF scores, and no racial or ethnic differences in these effects were observed in this subset analysis.

Previous studies have found moderate-to-strong correlations between FVC and patient-reported outcomes, such as the St George's Respiratory Questionnaire and the University of California, San Diego Shortness of Breath Questionnaire, in patients with various types of ILDs [13,21–24]. Therefore, therapeutic agents such as nintedanib that slow or prevent the progression of lung function decline [25] can be expected to have a stabilizing effect on (or reduce worsening of) patient symptoms and disease impacts. A previous analysis of the overall INBUILD population suggested that preserving lung function with nintedanib was beneficial in preventing the deterioration of symptoms and reducing the disease impacts in patients with PF-ILDs [13]. Furthermore, previous subgroup/subset analyses of the INBUILD trial showed that nintedanib was associated with a reduction in the rate of FVC decline and a decreased risk of clinical outcomes indicative of ILD progression in Japanese patients with PF-ILDs, consistent with the effects observed in the overall INBUILD population [14,15]. Therefore, it is reasonable that the effects of nintedanib on pulmonary fibrosis symptoms and impacts in Japanese patients were similar to those observed in the overall INBUILD population.

Both the current subset analysis and the overall INBUILD population analysis reported lower odds of deterioration in the L-PF symptoms cough and dyspnea domain score that met meaningful change thresholds in the nintedanib group. Cough, which is a common symptom in patients with ILD, is associated with significantly reduced FVC [26], and also correlates with a reduced HRQoL in patients with PF-ILDs [4,5,17,24,27,28]. Worse L-PF dyspnea scores at baseline and worsening L-PF dyspnea scores over 24 weeks were associated with an increased risk of ILD progression or death and other patient-relevant outcomes including acute exacerbation [29]; dyspnea is also associated with a reduced HRQoL [28]. In this context, the fact that nintedanib was associated with consistent reductions in the L-PF symptoms cough and dyspnea domain score in the current and overall INBUILD population analysis is significant and promising. The odds of deterioration in L-PF symptoms cough and dyspnea domain score that met meaningful change thresholds in the overall INBUILD population were lower in the nintedanib group than in the placebo group; OR: 0.65, 95% CI: 0.46, 0.92 for a change of ≥4 points and OR: 0.57, 95% CI: 0.40, 0.81 for a change of ≥5 points in L-PF symptoms cough domain score and OR: 0.67, 95% CI: 0.48, 0.94 for a change of ≥6 points and OR: 0.70, 95% CI: 0.50, 0.98 for a change of ≥7 points in L-PF symptoms dyspnea domain score [13].

One of the strengths of the INBUILD trial, and particularly the present subset analysis, is the use of the L-PF questionnaire to assess patient-reported outcomes, such as the symptoms and impacts of pulmonary fibrosis, which was developed specifically for patients with pulmonary fibrosis. In a consensus report based on the input from patients, clinicians, payers, and regulators, the L-PF questionnaire was considered to be the best (among nine reviewed instruments) at capturing the effect of PF-ILDs on patient wellbeing [5].

The key limitation of this analysis is its exploratory subset design, which was not specifically designed or powered to detect the effects of nintedanib on patient-reported symptoms and impacts in Japanese patients. However, the consistent results observed between this analysis and the overall INBUILD population across all L-PF scores suggest that the Japanese version of the L-PF questionnaire can be useful in assessing the progression and impacts of pulmonary fibrosis symptoms and in evaluating the effects of nintedanib in Japanese patients with PF-ILDs using patient-reported outcomes.

5. Conclusions

The present subset analysis findings suggest that nintedanib reduces the worsening of symptoms and impacts of pulmonary fibrosis in Japanese patients with PF-ILDs other than IPF. Further studies are needed to extend these results to Japanese patients with other PF-ILDs and to evaluate the utility of the L-PF questionnaire in Japanese clinical

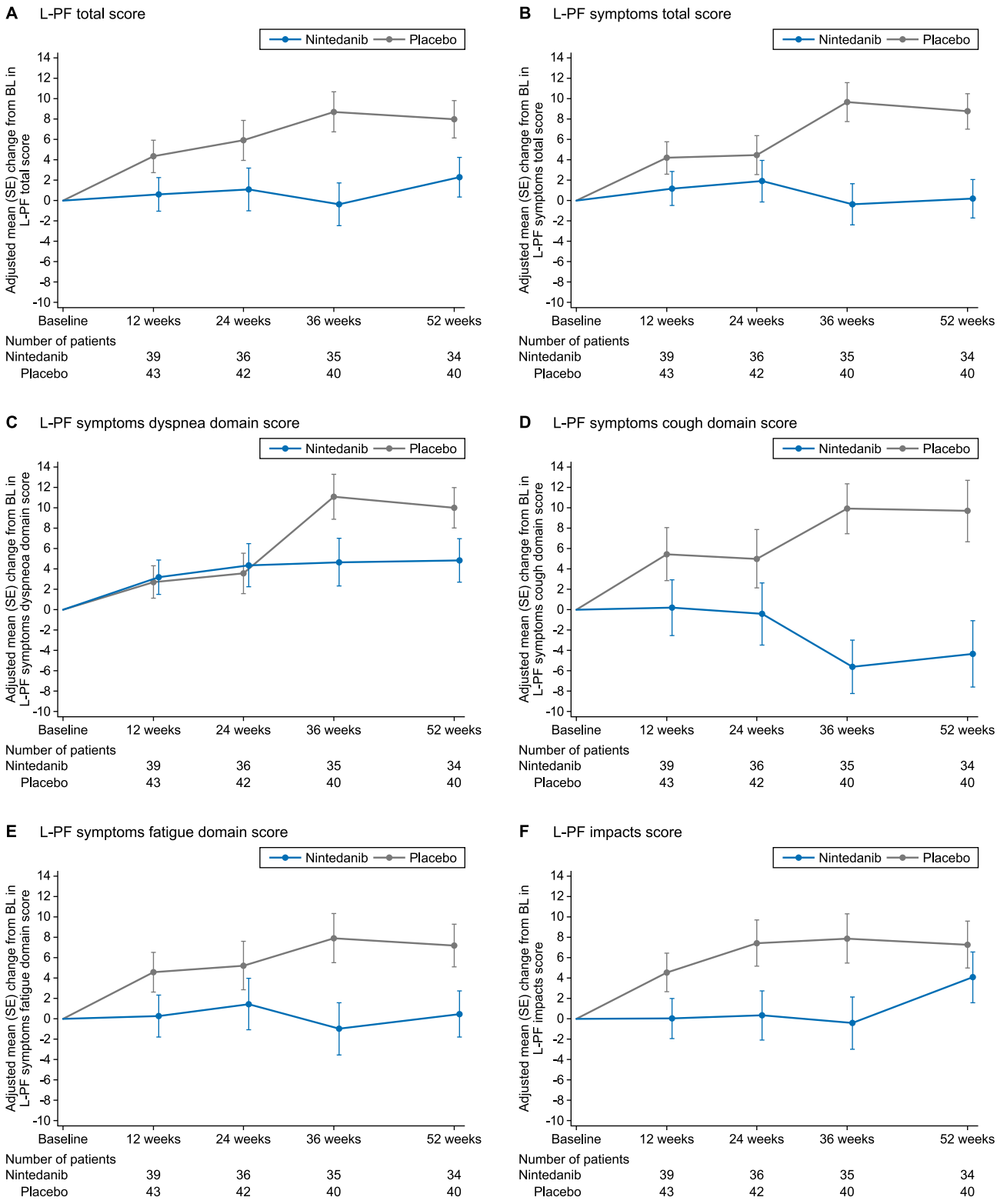

Fig. 3. Adjusted mean (standard error [SE]) change from baseline (BL) over 52 weeks in the Living with Pulmonary Fibrosis (L-PF) questionnaire (A) total, (B) symptoms total, (C) symptoms dyspnea domain, (D) symptoms cough domain, (E) symptoms fatigue domain, and (F) impacts scores in Japanese patients with usual interstitial pneumonia-like fibrotic pattern on high-resolution computed tomography.

practice and clinical trials.

Author contributions

Yoshikazu Inoue and Masataka Kuwana contributed to the conceptualization and methodology of the study. All authors contributed to the interpretation of study results. Yoshikazu Inoue, Hideya Kitamura, Masaki Okamoto, Takashi Ogura, Yasuhiko Nishioka, Masataka Kuwana and Takafumi Suda were study investigators. Atsushi Taniguchi, Tomohiro Ito and Klaus B. Rohr conducted the formal

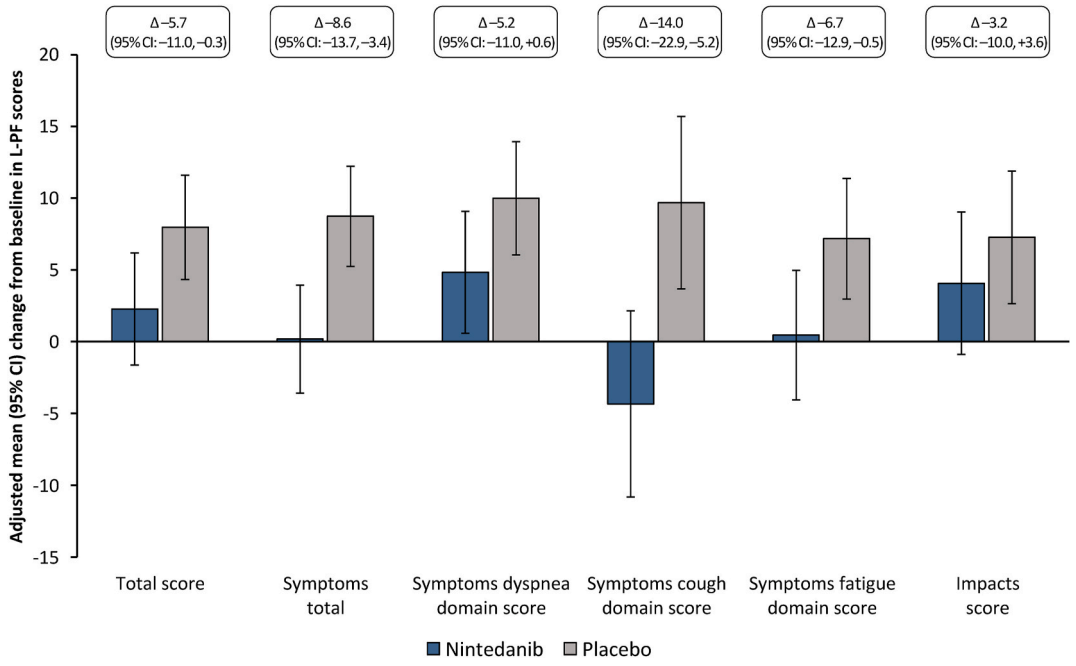

Fig. 4. Adjusted mean (95% confidence interval [CI]) change in the Living with Pulmonary Fibrosis (L-PF) questionnaire scores from baseline to week 52 in Japanese patients with usual interstitial pneumonia-like fibrotic pattern on high-resolution computed tomography. For each score, the adjusted mean between-group difference (Δ) and 95% CI is presented above the graph.

Table 2
Number of patients who met thresholds to differentiate patients who were stable or improved from those who deteriorated in L-PF symptoms dyspnea domain score at week 52.

	Nintedanib (n = 52)	Placebo (n = 56)
Threshold of ≥6 points		
Increase in score ≥6 points (worsening), n	18	25
OR (95% CI)	0.57 (0.24, 1.34)	
No increase in score ≥6 points (stability or improvement), n	34	31
OR (95% CI)	1.75 (0.75, 4.10)	
Threshold of ≥7 points		
Increase in score ≥7 points (worsening), n	17	22
OR (95% CI)	0.68 (0.29, 1.61)	
No increase in score ≥7 points (stability or improvement), n	35	34
OR (95% CI)	1.46 (0.62, 3.45)	

CI, confidence interval; L-PF, Living with Pulmonary Fibrosis; OR, odds ratio. 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.

Table 3
Number of patients who met thresholds to differentiate patients who were stable or improved from those who deteriorated in L-PF symptoms cough domain scores at week 52.

	Nintedanib (n = 52)	Placebo (n = 56)
Threshold of ≥4 points		
Increase in score ≥4 points (worsening), n	16	36
OR (95% CI)	0.27 (0.11, 0.64)	
No increase in score ≥4 points (stability or improvement), n	36	20
OR (95% CI)	3.71 (1.57, 8.77)	
Threshold of ≥5 points		
Increase in score ≥5 points (worsening), n	12	33
OR (95% CI)	0.23 (0.10, 0.56)	
No increase in score ≥5 points (stability or improvement), n	40	23
OR (95% CI)	4.32 (1.78, 10.51)	

CI, confidence interval; L-PF, Living with Pulmonary Fibrosis; OR, odds ratio. 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.

analyses. Yoshikazu Inoue, Atsushi Taniguchi, Tomohiro Ito and Klaus B. Rohr contributed to writing the original draft of the manuscript. All authors reviewed, edited, and approved the final manuscript.

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Ethical approval statement

The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, local regulations, and the protocol, which was approved by the independent ethics committees (Supplementary Table 1). All patients provided written informed consent prior to enrolment.

Data availability

Data are available on reasonable request. To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfil their role and obligations

as authors under the International Committee of Medical Journal Editors (ICMJE) criteria. Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (https://www.mystudywindow.com/msw/datasharing). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. On approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a period of 1 year, which may be extended on request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of informed consent. Researchers should use the https://vivli.org/link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resinv.2024.04.008.

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