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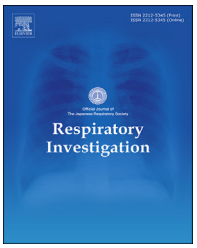

Original article

Effects of nintedanib on disease progression and safety in Japanese patients with progressive fibrosing interstitial lung diseases: Further subset analysis from the whole INBUILD trial

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ABSTRACT

Background: A previous subgroup analysis of data from the INBUILD trial showed that nintedanib reduced the annual rate of decline in forced vital capacity (FVC) in Japanese patients with progressive fibrosing interstitial lung diseases (PF-ILDs). The safety profile of nintedanib over 52 weeks in Japanese patients was similar to that of the overall population.
Methods: Using data from 108 Japanese patients with PF-ILDs who had received at least 1 dose of study medication in the INBUILD trial, we evaluated the effect of nintedanib on disease progression and assessed the safety profile over the whole trial period (i.e., a longer duration than the prior analysis) compared with placebo. ILD progression was defined as an absolute decline in FVC ≥10% predicted vs baseline.
Results: Over the whole trial, in Japanese patients with PF-ILDs, nintedanib numerically lowered the risk of progression of ILD or death (hazard ratio [HR], 0.66; 95% confidence

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CT, computed tomography; DLco, diffusing capacity of the lung for carbon monoxide; DMARD, disease-modifying anti-rheumatic drug; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; HR, hazard ratio; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; PF-ILD, progressive fibrosing interstitial lung disease; PY, patient-years; SSc, systemic sclerosis; uIIP, unclassifiable idiopathic interstitial pneumonia; UIP, usual interstitial pneumonia.

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intervals [CI]: 0.37, 1.16), acute exacerbation of ILD or death (HR, 0.28; 95% CI: 0.09, 0.83), and death (HR, 0.41; 95% CI: 0.11, 1.51). The most common adverse event over the whole trial in nintedanib-treated Japanese patients was diarrhea, which was manageable for most patients by dose reduction and interruption. The safety profile of nintedanib in this longer duration analysis was consistent with that previously reported.

Conclusions: In this analysis of data from Japanese patients with PF-ILDs, nintedanib nominally reduced the risk of clinically meaningful outcomes reflecting disease progression, including death, over the whole trial, and no new safety concerns were observed.

Clinical trial registration: ClinicalTrials.gov NCT02999178.

1. Introduction

More than 200 different parenchymal pulmonary conditions constitute the group of disorders collectively termed interstitial lung diseases (ILDs) [1]. Most of these conditions are rare; prevalence estimates of overall ILDs are 74–76/100,000 in the United States and Europe, and those of the common fibrotic ILDs are 8.2–30.2/100,000 [2]. Prevalence rates in Asia are largely unknown due to a lack of epidemiologic studies in this region [3,4]. In clinical practice, within the spectrum of fibrosing ILDs, a subset of patients continues to have ILD progression despite appropriate disease management, and are categorized as having the progressive fibrosing phenotype [1,5]. An analysis of online survey data from several countries reported that 18–32% of patients with ILDs other than idiopathic pulmonary fibrosis (IPF) may develop progressive fibrosis, and the time between symptom onset and death was 61–80 months [6].

Nintedanib is an intracellular tyrosine kinase inhibitor indicated for the treatment of chronic fibrosing ILDs with a progressive phenotype [7–9]. The double-blind, placebo-controlled, phase 3 INBUILD trial in patients with progressive fibrosing ILDs (PF-ILDs) other than IPF demonstrated that nintedanib 150 mg twice daily (BID) reduced the annual rate of decline in forced vital capacity (FVC) compared with placebo by 57% over 52 weeks, with adverse events manageable for most patients [10,11].

PF-ILD is a chronic and irreversible fibrotic lung disease requiring long-term treatment [12,13]. Notably, the INBUILD trial comprised two parts: the duration of Part A was 52 weeks, and Part B was a variable treatment period for each patient which continued beyond 52 weeks until the last patient completed the trial [10,14]. Thus, the data accrued beyond 52 weeks from patients with PF-ILDs in the INBUILD trial can provide critical support for the longer-term effectiveness and safety profile of nintedanib. A prior analysis using the data collected over the whole INBUILD trial (i.e., Parts A + B) showed that nintedanib reduced the risk of events reflecting the progression of ILD compared with placebo; moreover, the safety profile was consistent with that observed over 52 weeks [15].

A previous Japanese subgroup analysis of data from Part A of the INBUILD trial indicated no heterogeneity in treatment effect on the annual rate of decline in FVC between Japanese and non-Japanese patients, and the safety profile over 52 weeks in Japanese patients was also consistent with the overall trial population [16]. However, there were several differences between the overall population and the Japanese subpopulation in terms of baseline demographics, including the percentage of patients with a usual interstitial pneumonia (UIP)-like fibrotic pattern on high-resolution computed tomography (HRCT), and the percentages of patients with each ILD (i.e., unclassifiable idiopathic interstitial pneumonia [uIIP], hypersensitivity pneumonitis [HP], and idiopathic nonspecific interstitial pneumonia [NSIP]). As several previous studies have reported that increased mortality may be associated with an imaging pattern of UIP on HRCT or presence of specific ILD subtype (e.g., uIIP) [17–24], we considered that further analysis of the events indicating ILD progression over the whole INBUILD trial (Parts A + B; i.e., a longer duration than the prior Japanese subset analysis) was needed to confirm the consistency of the results compared with the overall population. Here, we report the effect of nintedanib on three clinically meaningful outcomes reflecting ILD progression, including progression of ILD or death, compared with placebo, and the safety profile of treatment, in Japanese patients with PF-ILDs.

2. Patients and methods

2.1. Study design

The study design for the INBUILD trial (NCT02999178) has been reported [10,14]. In summary, this was a randomized, double-blind, placebo-controlled, parallel-group trial of 663 patients with PF-ILDs conducted at 153 sites in 15 countries. The trial was performed in accordance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, local regulations, and the protocol, which was approved by local authorities (see also Supplemental Table 1). All patients provided written informed consent prior to enrolment.

2.2. Patients

Full eligibility criteria have been published [10]. In brief, key inclusion criteria were age ≥18 years (≥20 years in Japan) who had a physician-diagnosed fibrosing ILD other than IPF with features of fibrosis affecting more than 10% of lung volume on HRCT confirmed by central review. Patients were required to meet ≥1 of the following criteria for progression of ILD at any point within the 24 months before screening, despite management considered appropriate in clinical practice for the individual ILDs (excluding nintedanib or pirfenidone treatment): 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. Patients were also required to have FVC of ≥45% of the predicted value and diffusing capacity of the lung for carbon monoxide (DLco) (corrected for hemoglobin) of 30% to <80% of the predicted value.

2.3. Treatment

Patients were randomly assigned 1:1 to receive oral nintedanib (150 mg BID) or placebo, further stratified by HRCT fibrosing pattern (a UIP-like pattern or other fibrotic patterns) in a 2:1 ratio. In Part A, all patients were treated for 52 weeks. In Part B, each patient was treated for a variable treatment period beyond 52 weeks during which patients continued to receive either nintedanib or placebo until all participants had completed the trial. Unless patients withdrew their consent, all patients, including those who discontinued the trial medication, were asked to attend all visits as originally planned. Patients still receiving trial medication at the end of Part B were allowed to enter INBUILD-ON, an open-label extension of the INBUILD trial. The first database lock in the INBUILD trial occurred after the last patient had completed the week 52 visit, with final database lock occurring after all patients had either completed the follow-up visit or entered the INBUILD-ON extension trial.

2.4. Outcomes and statistical methods

Study endpoints included time to progression of ILD or death (where progression was defined as an absolute decline in FVC ≥10% predicted), time to first acute ILD exacerbation or death, and time to death over the whole trial [10]. Herein, we report these event outcomes over the whole trial (up to the final database lock) in all Japanese patients, and in the subset of Japanese patients with a UIP-like fibrosis pattern on HRCT (a prespecified coprimary population in the overall population analysis).

All analyses were conducted in patients who had received at least 1 dose of study medication. All endpoints for the Japanese patients were considered exploratory in nature and no *P*-values were calculated. Time-to-event data were calculated based on a Cox's regression model with terms for treatment used to derive the hazard ratio (HR) and 95% confidence intervals (CI) (stratified by HRCT pattern). Kaplan-Meier plots by treatment group were produced to visualize the data. Analyses for adverse events and laboratory parameters were descriptive. Adverse events in the Japanese population were coded using the Medical Dictionary for Regulatory Activities version 22.0. Diarrhea severity was classified using the Common Terminology Criteria for Adverse Events version 4.03. All analyses were prespecified and conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

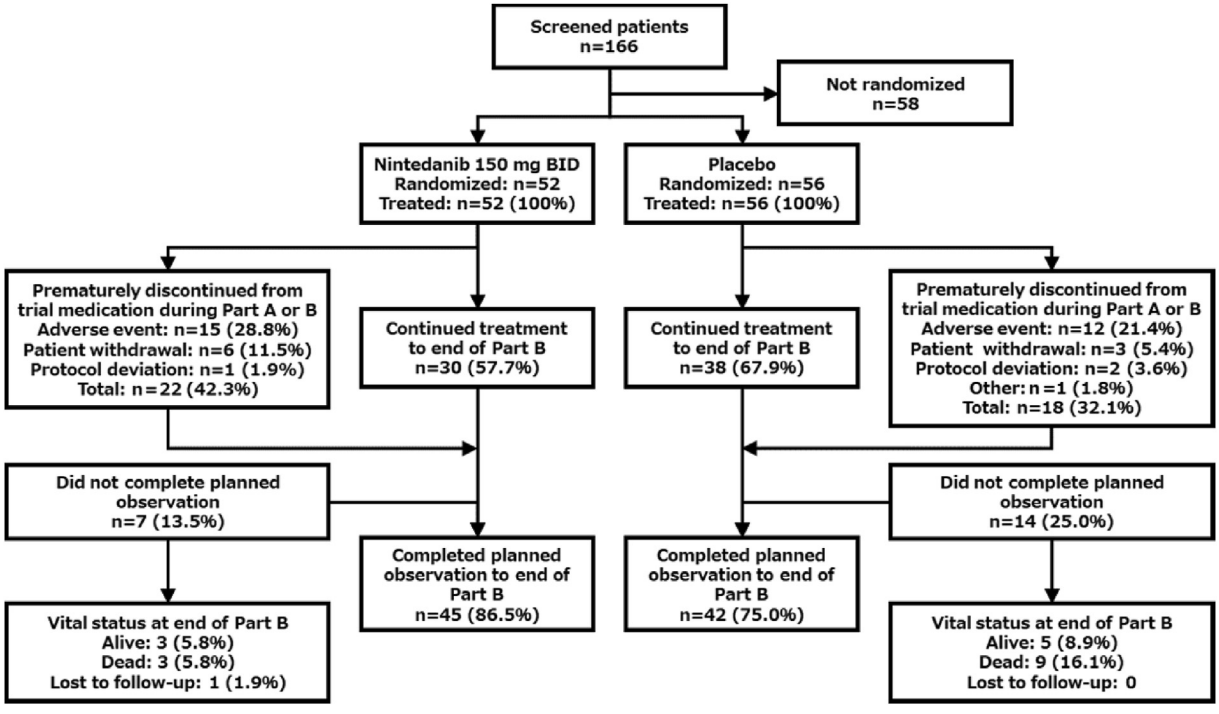

Fig. 1 – Patient disposition over the whole trial (Parts A and B) for Japanese patients in the INBUILD trial. BID, twice daily.

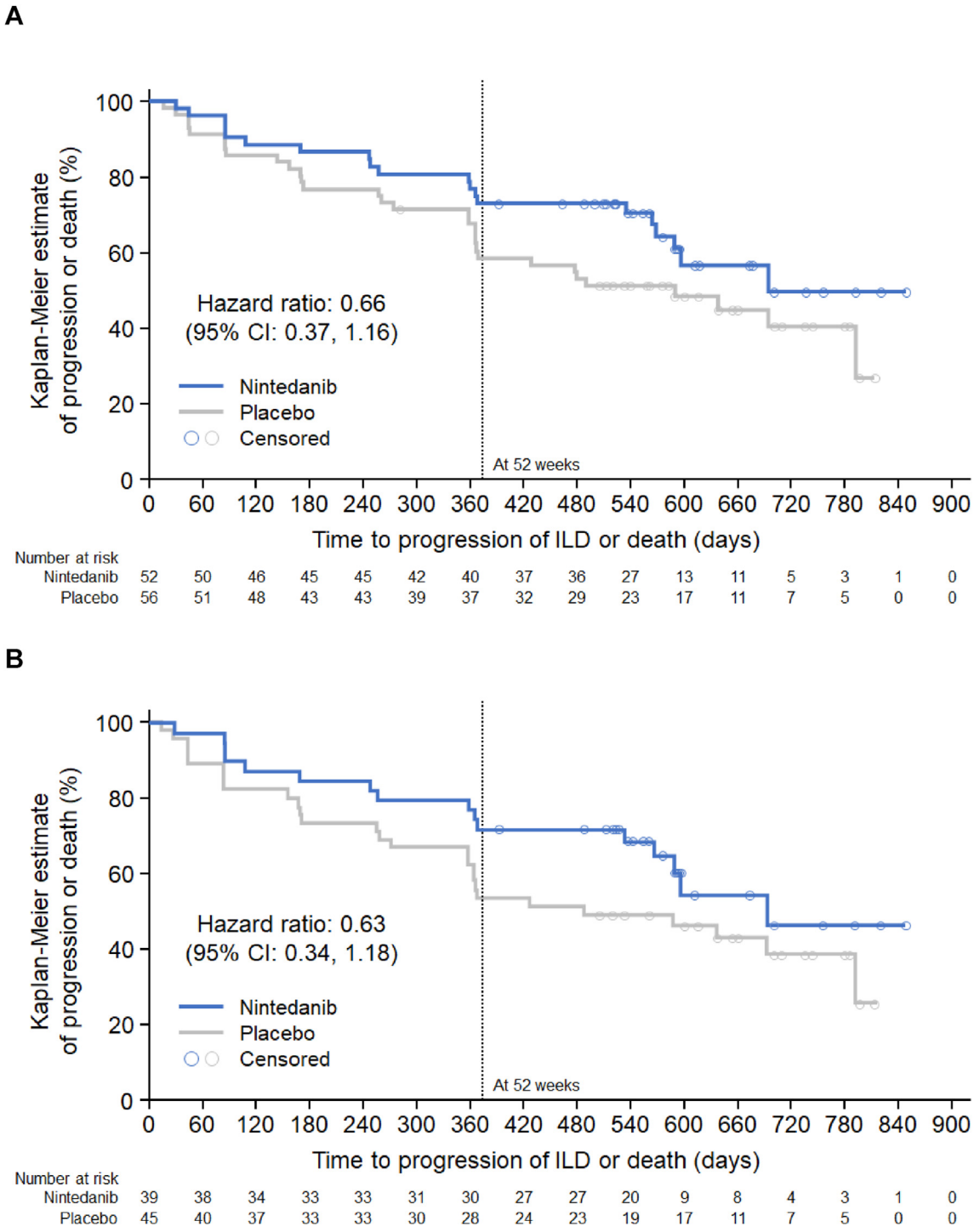

Fig. 2 – Time to progression of ILD (absolute decline in FVC ≥10% predicted) or death over the whole trial in (A) all Japanese patients and (B) Japanese patients with a UIP-like fibrotic pattern.
CI, confidence intervals; FVC, forced vital capacity; ILD, interstitial lung disease; UIP, usual interstitial pneumonia.

3. Results

3.1. *Patients*

A total of 108 Japanese patients received study medication (nintedanib, n = 52; placebo, n = 56) and were included in this analysis. The detailed baseline characteristics of Japanese patients have been reported elsewhere [16]. In brief, the mean age was 68.1 years, the mean FVC % predicted was 69.5, and the mean DLco % predicted was 44.4. Eighty-four (77.8%) Japanese patients had a UIP-like fibrotic pattern on HRCT, and the most common clinical ILD diagnoses were uIIP (n = 39; 36.1%), HP (n = 14; 13.0%) and NSIP (n = 14; 13.0%). Overall 33 (30.6%) Japanese patients were diagnosed with an autoimmune ILD.

Table 1 – Time-to-event results in Japanese patients over the whole INBUILD trial.

Number of patients meeting each time-to-event outcome	All Japanese patients			Patients with a UIP-like fibrotic pattern on HRCT		
	Nintedanib 150 mg BID (n = 52)	Placebo (n = 56)	Nintedanib vs placebo HR (95% CI)	Nintedanib 150 mg BID (n = 39)	Placebo (n = 45)	Nintedanib vs placebo HR (95% CI)
Progression of ILD or death, n (%)	20 (38.5)	31 (55.4)	0.66 (0.37, 1.16)	16 (41.0)	27 (60.0)	0.63 (0.34, 1.18)
Progression of ILD, n	17	28		13	24	
Death, n	3	3		3	3	
First acute exacerbation of ILD or death, n (%)	4 (7.7)	16 (28.6)	0.28 (0.09, 0.83)	4 (10.3)	14 (31.1)	0.33 (0.11, 1.02)
First acute exacerbation, n	3	9		3	7	
Death, n	1	7		1	7	
Death, n (%)	3 (5.8)	9 (16.1)	0.41 (0.11, 1.51)	3 (7.7)	9 (20.0)	0.41 (0.11, 1.51)

BID, twice daily; CI, confidence interval; CT, computed tomography; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; UIP, usual interstitial pneumonia.
The data indicate the number of patients (n, or n [%]) who met each time-to-event outcome over the whole INBUILD trial. Only the event occurring first for each outcome was counted. Acute exacerbation of ILD in the INBUILD trial was defined as acute and clinically significant respiratory deteriorations which were characterized by evidence of new widespread alveolar abnormality with all of the following: acute worsening or development of dyspnea typically less than one month duration, CT with new bilateral ground-glass opacity and/or consolidation, superimposed on a background pattern consistent with fibrosing ILD, and deterioration not fully explained by cardiac failure or fluid overload.

Overall, 45 patients (86.5%) in the nintedanib group and 42 patients (75.0%) in the placebo group completed the planned observation time (Fig. 1); the most common reason for non-completion was death (nintedanib, n = 3; placebo, n = 9). At least 1 dose reduction was reported in 28 patients (53.8%) in the nintedanib group and 0 patients in the placebo group; 28 patients (53.8%) in the nintedanib group and 6 (10.7%) in the placebo group had at least 1 dose interruption, generally to manage adverse events. In the nintedanib and placebo groups, 22 patients (42.3%) and 18 patients (32.1%), respectively, prematurely discontinued trial medication; the main reason was adverse events (nintedanib, n = 15; placebo, n = 12). The mean (standard deviation) duration of exposure was 15.9 (6.9) and 17.1 (7.2) months in the nintedanib and placebo group, respectively. Use of restricted medication during the whole trial is shown in Supplemental Table 2.

3.2. *Time to progression of ILD (absolute decline in FVC ≥10% predicted vs baseline) or death*

Over the whole trial, the percentage of Japanese patients who either had progression of ILD or died was 38.5% (n = 20) in the nintedanib group and 55.4% (n = 31) in the placebo group; this was numerically lower with nintedanib versus placebo (Fig. 2A, Table 1). The HR tended to favor nintedanib over placebo (HR, 0.66; 95% CI: 0.37, 1.16). This trend in favor of nintedanib was also observed in the subset of patients with a UIP-like fibrotic pattern (HR, 0.63; 95% CI: 0.34, 1.18) (Fig. 2B, Table 1).

3.3. *Time to first acute exacerbation of ILD or death*

The percentage of patients who either had an acute exacerbation or died was 7.7% (n = 4) in the nintedanib group and 28.6% (n = 16) in the placebo group; this was numerically lower with nintedanib versus placebo (Fig. 3A, Table 1). The HR tended to favor nintedanib over placebo (HR, 0.28; 95% CI: 0.09, 0.83). A similar trend was also observed in the patients with a UIP-like fibrotic pattern (HR, 0.33; 95% CI: 0.11, 1.02) (Fig. 3B, Table 1).

3.4. *Time to death*

In the Japanese subset, 5.8% (n = 3) in the nintedanib group and 16.1% (n = 9) in the placebo group died during the whole trial (Fig. 4A, Table 1). The main cause of death in both treatment groups was due to respiratory events (as determined by the adjudication committee). The percentage of patients who died was numerically lower in the nintedanib group than in the placebo group, and the HR tended to favor nintedanib (HR, 0.41; 95% CI: 0.11, 1.51). In the subset with a UIP-like fibrotic pattern, 7.7% (n = 3, nintedanib) and 20.0% (n = 9, placebo) died during the whole trial (HR, 0.41; 95% CI: 0.11, 1.51) (Fig. 4B, Table 1).

3.5. *Safety*

All Japanese patients, in both treatment groups, had at least 1 adverse event. The most common was diarrhea, which was more frequent in the nintedanib group (249 events/100 patient-years [PY]) than in the placebo group (34/100 PY) (Table 2). In most cases, diarrhea severity was Grade 1 (nintedanib, n = 32; placebo, n = 19) or Grade 2 (nintedanib, n = 9; placebo, n = 1); Grade 3 events were rare (nintedanib, n = 3; placebo, n = 0) and no patients had Grade ≥4 diarrhea. Other adverse events reported more frequently with nintedanib versus placebo were nausea, vomiting, hepatic function abnormal, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and weight decreased; conversely, ILD (which included ILD deterioration) was less frequently reported with nintedanib versus placebo. Eleven patients (21.2%) in the nintedanib group had elevations

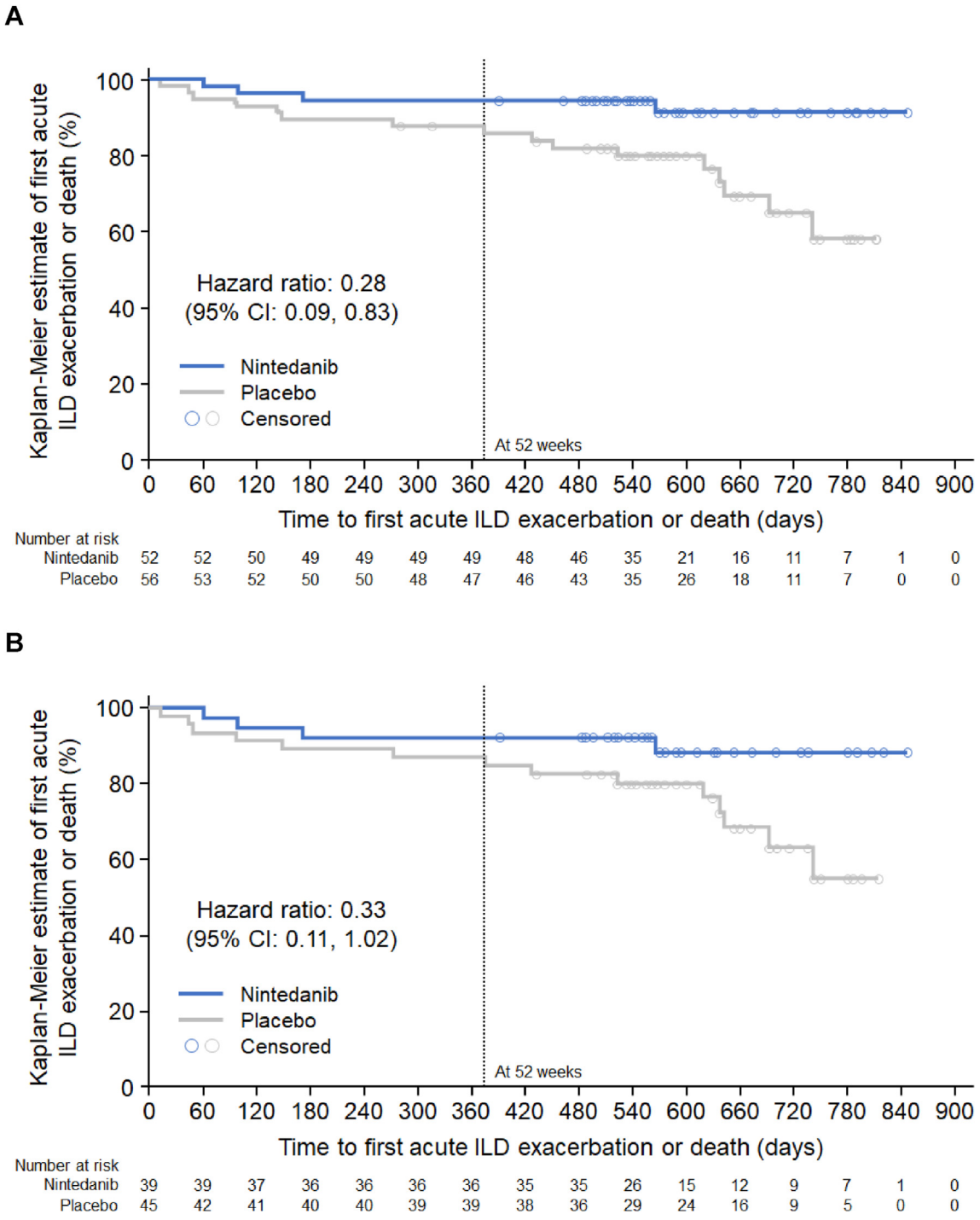

Fig. 3 – Time to first acute exacerbation of ILD or death over the whole trial in (A) all Japanese patients and (B) Japanese patients with a UIP-like fibrotic pattern. CI, confidence intervals; CT, computed tomography; ILD, interstitial lung disease; UIP, usual interstitial pneumonia. Acute exacerbation of ILD in the INBUILD trial was defined as acute and clinically significant respiratory deteriorations which were characterized by evidence of new widespread alveolar abnormality with all of the following: acute worsening or development of dyspnea typically less than one month duration, CT with new bilateral ground-glass opacity and/or consolidation, superimposed on a background pattern consistent with fibrosing ILD, and deterioration not fully explained by cardiac failure or fluid overload.

in ALT and/or AST of ≥3 × the upper limit of the normal range, compared with 0 patients in the placebo group. Most ALT/AST elevations returned to the normal range on dose reduction, after treatment interruption or discontinuation, or spontaneously on continued treatment. There were no patients in either treatment group who met the criteria for Hy's law.

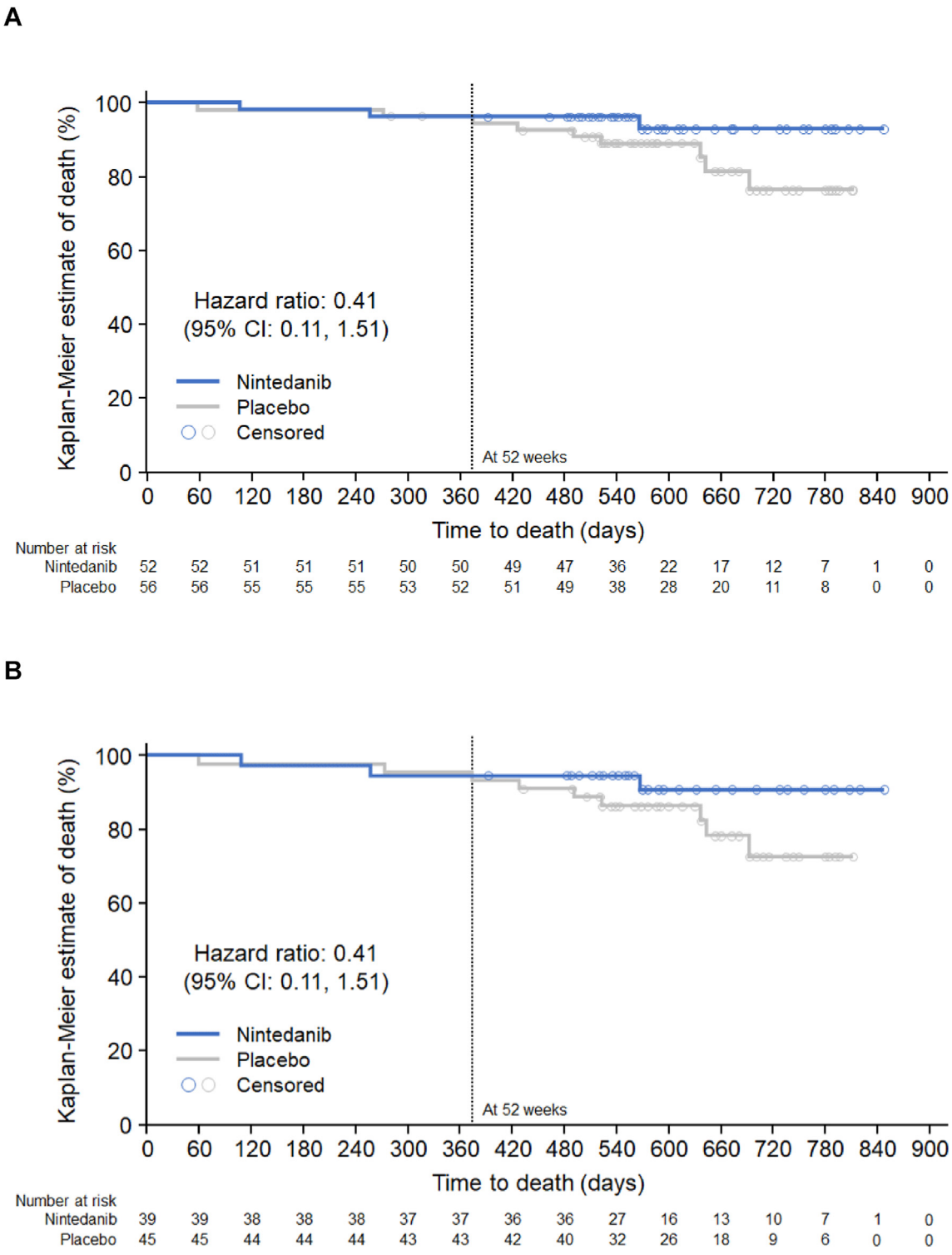

Fig. 4 – Time to death over the whole trial in (A) all Japanese patients and (B) Japanese patients with a UIP-like fibrotic pattern. CI, confidence intervals; UIP, usual interstitial pneumonia.

Adverse events leading to permanent dose reduction of trial medication occurred in 26 patients receiving nintedanib (50%) and none receiving placebo; the most common were diarrhea (n = 10), followed by hepatic function abnormal (n = 7) and AST increased (n = 5). Adverse events leading to permanent discontinuation of trial medication occurred in 15 patients receiving nintedanib (28.8%) and 12 receiving placebo (21.4%); the most common were ILD (nintedanib, n = 3; placebo, n = 7), followed by diarrhea (nintedanib, n = 3; placebo, n = 0), hepatic function abnormal (nintedanib, n = 2; placebo, n = 0) and drug-induced liver injury (nintedanib, n = 2; placebo, n = 0).

Table 2 – Frequently reported adverse events in Japanese patients over the whole INBUILD trial.

Adverse events	Nintedanib 150 mg BID (n = 52)		Placebo (n = 56)	
	n (%)	Rate per 100 PY	n (%)	Rate per 100 PY
Diarrhea	44 (84.6)	249	20 (35.7)	34
Nasopharyngitis	21 (40.4)	43	21 (37.5)	36
Nausea	15 (28.8)	27	1 (1.8)	1
Hepatic function abnormal	13 (25.0)	24	2 (3.6)	3
Interstitial lung disease	12 (23.1)	18	26 (46.4)	40
AST increased	9 (17.3)	15	1 (1.8)	1
ALT increased	8 (15.4)	13	1 (1.8)	1
Vomiting	8 (15.4)	13	0	0
Bronchitis	8 (15.4)	13	7 (12.5)	9
Pneumonia	8 (15.4)	12	6 (10.7)	8
Weight decreased	7 (13.5)	11	3 (5.4)	4
Constipation	7 (13.5)	10	12 (21.4)	16
Insomnia	5 (9.6)	7	8 (14.3)	10
Back pain	4 (7.7)	6	9 (16.1)	12

ALT. alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; PY, patient-years.
Adverse events that were reported with an incidence rate of >10 events per 100 PY in either treatment group are shown. Adverse events in the Japanese population were coded using the Medical Dictionary for Regulatory Activities version 22.0.

Serious adverse events occurred in 29 patients receiving nintedanib (55.8%, 54 events/100 PY) and 36 patients receiving placebo (64.3%, 65/100 PY). The most common were ILD (nintedanib, n = 10 [19.2%, 15/100 PY]; placebo, n = 25 [44.6%, 39/100 PY]), and pneumonia (nintedanib, n = 5 [9.6%, 7/100 PY]; placebo, n = 2 [3.6%, 3/100 PY]).

4. Discussion

This subset analysis of all available data over the full duration (Parts A + B) of the INBUILD trial adds further support to the findings that nintedanib slows progression of ILD in Japanese patients with non-IPF PF-ILDs. Nintedanib was associated with nominal decreases in the risk of progression of ILD or death, acute exacerbation of ILD or death, or death in time-to-event analyses over the whole trial period (i.e., a longer duration than the prior analysis). The safety profile of nintedanib in Japanese patients was consistent with that observed in the INBUILD overall population, as well as in other clinical trials of nintedanib in IPF and SSc-ILD [10,15,25,26]. As with similar analyses of nintedanib-treated Japanese subgroups with IPF and SSc-ILD [27,28], and the previous Japanese INBUILD subanalysis over 52 weeks [16], no new safety concerns were observed.

Differences in baseline clinical characteristics (specifically, the proportions with a UIP-like fibrotic pattern, and with each ILD subtype) between the overall INBUILD population and the Japanese subpopulation [10,16] suggested that the Japanese subset might be at higher risk of ILD progression [17–24]. With this subset analysis, we show that despite these differences, nintedanib numerically reduced the risk of the outcomes indicating further progression of ILD over the whole trial in Japanese patients, irrespective of fibrotic patterns; this was consistent with the overall INBUILD population [15]. Previous reports have shown that absolute decline in FVC ≥10% predicted is predictive of mortality in patients with various ILDs [29–32]. It has also been reported that acute exacerbation is associated with increased mortality in patients with ILDs and that patients with FVC decline are more likely to experience an acute exacerbation [33–38]. A prespecified subgroup analysis in the INBUILD trial showed consistent treatment effects on FVC in patients with PF-ILDs across fibrotic patterns and the ILD diagnosis groups [10,39]. In addition, a consistent treatment effect of nintedanib on FVC was also observed between Japanese and non-Japanese patients, despite several differences in baseline characteristics [16]. Thus, it may be reasonable that the effect of nintedanib to numerically reduce the risk of clinically meaningful outcomes over the whole trial was observed in this Japanese subset in spite of differences in baseline characteristics.

The HR for the risk of acute exacerbation of ILD or death was numerically lower in the Japanese population (HR, 0.28; 95% CI: 0.09, 0.83) than in the overall INBUILD population (HR, 0.67; 95% CI: 0.46, 0.98) [15]. However, the number of events was small, and no definitive conclusions can be drawn. Additional studies will be needed to confirm this point.

In the previously published 52-week analysis of the Japanese INBUILD subgroup, the mean duration of exposure was 10.7 months in both treatment groups [16]; in the current analysis, this was extended to 15.9 and 17.1 months in the nintedanib and placebo groups, respectively. The safety profile of nintedanib in Japanese patients over the whole trial was consistent with previous reports, including the overall INBUILD population over both 52 weeks and the whole trial [10,15,16,25–28]. Although adverse events leading to permanent dose reduction, and diarrhea and hepatic function abnormal were reported more frequently in Japanese patients treated with nintedanib compared with the overall INBUILD nintedanib-treated population [15], these trends are similar to those of the 52-week analysis [16], and of the Japanese versus overall INPULSIS trial populations of patients with IPF [27].

In this analysis, most cases of diarrhea were mild or moderate and manageable. A previous exposure-safety analysis of nintedanib in patients with chronic fibrosing ILDs showed the administered dose was a better predictor of diarrhea than plasma exposure [40]. Therefore, management of diarrhea by dose reduction or treatment interruption with symptomatic treatment is indispensable to enable patients to continue treatment with nintedanib. Most hepatic adverse events in this analysis were also manageable, with liver enzymes normalizing spontaneously on continued treatment or following dose modification or discontinuation. While the exposure-safety analysis of nintedanib indicated a weak-to-moderate correlation between plasma exposure and liver enzyme elevations, this does not warrant *a priori* dose adjustment [40]. Although a population pharmacokinetic analysis showed that Asian race, low body weight and age

were associated with a small-to-moderate increase in nintedanib plasma exposure, each of these covariates had a lesser effect on nintedanib plasma exposure compared with interpatient variability [41]. In addition, in an exposure-efficacy analysis, a 150 mg BID dose of nintedanib resulted in efficacious plasma exposure levels close to the maximum drug effect irrespective of baseline characteristics including Asian race, body weight and age [42]. Therefore, periodic monitoring of liver enzyme levels in all patients and dose adjustment/interruption to manage hepatic adverse events is also critical for patients to benefit from long-term nintedanib treatment.

The limitations of this analysis are related to the exploratory subset design. The INBUILD trial was not powered to detect the effect of nintedanib on clinically meaningful outcomes in the Japanese subset, and statistical significance was not calculated. However, opportunities to conduct adequately powered studies in Japanese patients with rare diseases such as PF-ILD are limited and may not be practically feasible. Despite the limitations, these results in Japanese patients over the whole trial are consistent across outcomes and with the INBUILD overall population, providing physicians with valuable longer-term information about the effect on disease progression and safety profile of nintedanib in Japanese patients with PF-ILDs compared with placebo.

5. Conclusions

In Japanese patients with PF-ILDs other than IPF in the INBUILD trial, nintedanib nominally reduced the risk of clinically meaningful outcomes over the whole trial compared with placebo. The results of the prespecified analyses conducted in this subset were similar to those observed in the INBUILD overall population over the whole trial. The safety profile was consistent with prior reports, and no new safety concerns were observed.

Ethics approval and consent to participate

The INBUILD study was approved by the Ethics Committees of each participating institution (Supplemental Table 1). All patients provided written informed consent prior to enrolment in the study.

Funding

The INBUILD study was funded by Boehringer Ingelheim.

Data availability statement

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 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. Upon 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 upon 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 link at https://vivli.org/to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

Conflict of interest

TO has received research funding and lecture fees from Nippon Boehringer Ingelheim Co., Ltd. and lecture fees from Shionogi & Co., Ltd.

TS has received research funding and lecture fees from Nippon Boehringer Ingelheim Co., Ltd. and lecture fees from AstraZeneca K.K.

NI has nothing to declare.

YN has received lecture fees from Boehringer Ingelheim Co., Ltd.

AA has received lecture fees and travel expense from Boehringer Ingelheim Co., Ltd.

MO has received lecture fees from Boehringer Ingelheim Co., Ltd.

AT and TI are employees of Nippon Boehringer Ingelheim Co., Ltd.

KBR is an employee of Boehringer Ingelheim International GmbH.

YI was a member of the Industry Advisory Committee for Asahi Kasei Corporation, Shionogi & Co., Ltd., Taiho Pharmaceutical Co., Ltd., and SAVARA Inc, and a member of the Clinical Trial Steering Committee for Boehringer Ingelheim Co., Ltd. and Roche Products Ltd.

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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.2022.06.009.

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