



Early View

Original research article

Nintedanib in children and adolescents with fibrosing interstitial lung diseases

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Nintedanib in children and adolescents with fibrosing interstitial lung diseases

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Abstract

Childhood interstitial lung disease comprises a spectrum of rare ILDs affecting infants, children and adolescents. Nintedanib is a licensed treatment for pulmonary fibrosis in adults. The primary objectives of the InPedILD trial were to determine the dose-exposure and safety of nintedanib in children and adolescents with fibrosing ILD.

Patients aged 6–17 years with fibrosing ILD on HRCT and clinically significant disease were randomised 2:1 to receive nintedanib or placebo for 24 weeks then open-label nintedanib. Dosing was based on weight-dependent allometric scaling. Co-primary endpoints were the area under the plasma concentration-time curve at steady state ($AUC_{T,ss}$) at weeks 2 and 26 and the proportion of patients with treatment-emergent adverse events at week 24.

Twenty-six patients received nintedanib and 13 placebo. The geometric mean (gCV%) $AUC_{T,ss}$ for nintedanib was 175 ug*h/L (85.1) in patients aged 6–11 years and 160 ug*h/L (82.7) in patients aged 12–17 years. In the double-blind period, adverse events were reported in 84.6% of patients in each treatment group. Two patients discontinued nintedanib due to adverse events. Diarrhoea was reported in 38.5% and 15.4% of the nintedanib and placebo groups, respectively. Adjusted mean (SE) changes in FVC % predicted at week 24 were 0.3 (1.3) in the nintedanib group and -0.9 (1.8) in the placebo group.

In conclusion, in children and adolescents with fibrosing ILD, a weight-based dosing regimen resulted in exposure to nintedanib similar to adults and an acceptable safety profile. These data provide a scientific basis for the use of nintedanib in this patient population.

Introduction

Childhood interstitial lung disease (chILD) comprises a spectrum of rare and heterogeneous lung disorders affecting infants, children and adolescents that may be associated with significant morbidity [1,2]. The pathophysiology of chILD often involves a genetic component, sometimes combined with exposure-related injury or autoimmune dysregulation, although in some cases the aetiology remains unknown [1, 3–6]. Some children with ILD develop pulmonary fibrosis. As in adults, in chILD, pulmonary fibrosis involves tissue damage, excessive deposition of extracellular matrix, and aberrant remodelling of the lung, although fibroblastic foci are not seen histologically in children with fibrosis [1,7]. In the absence of licensed drugs for the treatment of chILD, treatment typically involves immunomodulation [8], but the evidence to support this approach is lacking.

Nintedanib is an intracellular inhibitor of tyrosine kinases that inhibits processes fundamental to the progression of pulmonary fibrosis [9,10]. Randomised controlled trials demonstrated that in adults with idiopathic pulmonary fibrosis (IPF), other forms of progressive pulmonary fibrosis, and fibrosing ILD associated with systemic sclerosis, nintedanib consistently reduced the rate of decline in forced vital capacity (FVC), a surrogate measure of ILD progression in adults [11], compared with placebo, with an adverse event profile characterised predominantly by gastrointestinal events [12–15]. Based on the clinical efficacy of nintedanib in adults, and presumed similarities in the pathophysiology of fibrotic lung remodelling in adults and children, it was postulated that nintedanib may provide similar benefit in a paediatric population with clinically significant or progressive pulmonary fibrosis. As a confirmatory trial of the efficacy of nintedanib in paediatric patients was deemed not feasible, the InPedILD trial (ClinicalTrials.gov NCT04093024; Eudra-CT 2018-004530-14) was designed with the primary objectives of evaluating the dose-exposure and safety of nintedanib in children and adolescents with fibrosing ILD. In addition, data on efficacy endpoints were collected to support evaluation of the benefit-risk of nintedanib in the paediatric population.

Materials and Methods

Patients

The InPedILD trial enrolled children or adolescents aged 6–17 years with fibrosing ILD on a high-resolution computed tomography (HRCT) scan performed ≤ 12 months before screening, confirmed by central review (see Supplementary Material), FVC $\geq 25\%$ predicted and clinically significant disease [16]. Clinically significant disease was defined as a Fan score ≥ 3 [17] or documented evidence of clinical progression over any time frame. The Fan score assesses disease severity in children and adolescents with ILD based on symptoms, oxygen saturation and pulmonary hypertension; scores range from 1 to 5, with higher scores indicating greater disease severity [17]. Evidence of clinical progression was based on a relative decline in FVC $\geq 10\%$ predicted, a relative decline in FVC of 5–10% predicted with worsening symptoms, worsening fibrosis on HRCT, or other measures of clinical worsening attributed to progressive pulmonary fibrosis (e.g., increased oxygen requirement, decreased diffusion capacity). Key exclusion criteria are listed in the Supplementary Material.

Trial design

The InPedILD trial was a phase 3 trial conducted at 43 sites in 21 countries [16]. After a 4-week screening period, patients were randomised 2:1 to receive nintedanib or placebo using interactive response technology, stratified by age group (6–11 years, 12–17 years) (Figure 1). Dosing was based on weight-dependent allometric scaling. Starting doses were 50 mg, 75 mg, 100 mg, or 150 mg twice daily and the dose was adjusted during treatment based on the patient's weight (Table 1). Dose reductions to the dose below and treatment interruptions were permitted to manage adverse events. The lowest dose was 25 mg twice daily. Dose re-escalation was allowed within 4 weeks of dose reduction for adverse events considered related to trial drug, or within 8 weeks for adverse events not considered related to trial drug.

The trial consisted of a placebo-controlled double-blind period of 24 weeks followed by a variable period during which all patients received open-label nintedanib (Figure 1). Patients who prematurely discontinued study drug were asked to attend all visits as originally planned. Once ≥ 30 patients (including ≥ 20 patients aged 12–17 years) had completed pharmacokinetic sampling at week 26 or had prematurely discontinued the trial, recruitment was closed. Following confirmation that sufficient pharmacokinetic data had been collected, all patients were scheduled for an end-of-treatment visit, after which they entered a 4-week follow-up period or rolled over into an open-label extension trial in which all patients received nintedanib (InPedILD-ON; ClinicalTrials.gov NCT05285982; Eudra-CT 2020-005554-23).

A Steering Committee provided scientific advice on the design of the trial. A Safety Monitoring Committee reviewed pharmacokinetic and safety data to determine the safety profile and benefit-risk of nintedanib and advise on dose modification, additional assessments, and the appropriateness of further enrolment and continuation of the trial. An Adjudication Committee was established to adjudicate deaths due to cardiac, respiratory or other causes and review adverse events categorized as major adverse cardiovascular events. 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, EU directive 2001/20/EC/EU regulation 536/2014 and other relevant guidelines. The trial was initiated at each site (listed in the Supplementary Material) following approval by the respective institutional review board/independent ethics committee and competent authority according to national and international regulations. Written informed consent and assent (where applicable) were obtained prior to trial entry.

Endpoints

The co-primary endpoints were the area under the plasma concentration–time curve at steady state ($AUC_{T,ss}$) at week 2 of nintedanib treatment (i.e., at week 2 in patients randomised to receive nintedanib and at week 26 in patients randomised to receive placebo for 24 weeks followed by nintedanib) and the proportion of patients with treatment-emergent adverse events at week 24, which were defined as events with onset from the first intake of trial drug until the day prior to first intake of open-label nintedanib or the last intake of randomised treatment plus 28 days (whichever occurred first). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 25.

Pathological findings on bone imaging and stunted growth of the dental root on dental imaging were defined as adverse events of special interest. Secondary safety endpoints included the proportion of patients with pathological findings of epiphyseal growth plate on imaging and pathological findings on dental examination or imaging at week 24. Follow-up imaging of epiphyseal growth plates was only conducted in patients with open physes. Change from baseline in height-for-age z-score at week 24 was a further endpoint.

Secondary efficacy endpoints included changes in FVC % predicted, oxygen saturation (SpO_2) at rest, 6-minute walk test (6MWT) distance and Pediatric Quality of Life™ (PedQL™) questionnaire scores at week 24. Spirometry was performed using standardised spirometers supplied to each site and according to ATS/ERS guidelines [18]. FVC % predicted values were calculated using equations published by the European Respiratory Society Global Lung Function Initiative [19]. The PedsQL questionnaire comprised the young child report (5–7 years), the child report (8–12 years) and the teen report (>12 years), as well as a parent report for each age range; each of these scores ranges from 0 to 100, with higher scores indicating better health-related quality of life [20].

Analyses

For the primary pharmacokinetic analysis, $AUC_{T,ss}$ was calculated using non-compartmental and compartmental analyses and descriptive statistics. In patients randomised to nintedanib, the $AUC_{T,ss}$ at week 2 was used; if this value was missing, the value at week 26 was used. In patients randomised to placebo, the $AUC_{T,ss}$ at week 26 (corresponding to week 2 of nintedanib treatment) was used. Pharmacokinetic analyses were conducted in patients who received ≥ 1 dose of trial medication and provided evaluable data for ≥ 1 pharmacokinetic endpoint without protocol violations relevant to the evaluation of pharmacokinetics. Safety analyses were conducted in patients who received ≥ 1 dose of trial medication. Adjusted mean changes from baseline in FVC % predicted, SpO_2 , 6MWT distance, PedsQL questionnaire scores and height-for-age z-score at week 24 were analysed using a mixed model for repeated measures, with fixed categorical effects of treatment at each visit and age group and fixed continuous effects of baseline at each visit, and random effect for patient. Adverse events are presented descriptively.

Sample size was calculated based on the evaluation of the primary pharmacokinetic endpoint and the need for the clearance parameter to be estimated with adequate precision. Assuming a coefficient of variation (CV) of 70.8% (based on the geometric CV of apparent clearance of nintedanib in the plasma at steady state [CL/F_{ss}] following extravascular multiple dose administration), ≥ 20 patients with pharmacokinetic measurements per age group (6–11 years and 12–17 years) would be needed to achieve $\geq 80\%$ probability (loosely referred to as power [21]) of having the 95% confidence interval of the CL/F_{ss} and the $AUC_{T,ss}$ within 60% and 140% of the geometric mean estimate. Based on the inclusion criteria and a preliminary feasibility assessment, it was anticipated that the study would only enrol enough patients aged ≥ 12 years to achieve this probability; however, pharmacokinetic data from children aged 6–11 years were also collected and analysed. A sample size of ≥ 30 patients (≥ 10 aged 6–11 years, ≥ 20 aged 12–17 years) was targeted.

Results

Patients

Of 87 patients screened, 39 patients (12 aged 6–11 years, 27 aged 12–17 years) were randomised and treated (26 with nintedanib, 13 with placebo) (Figure 2, Table S1). Baseline characteristics were generally balanced between the treatment groups (Table 2). The majority of patients were female (61.5%) and white (79.5%). Mean (SD) age was 12.6 (3.3) years, weight was 42.2 (17.8) kg and FVC was 59.4 (21.9) % predicted. The most common diagnostic category was surfactant protein deficiency (30.8%). The most frequent criterion met for clinically significant disease was a Fan score ≥ 3 (59.0%) (Table S2).

Exposure

Mean (SD) exposure to trial medication during the double-blind period was 22.3 (4.8) weeks in the nintedanib group and 22.6 (4.2) weeks in the placebo group (Table 3). During this period, four patients (15.4%) in the nintedanib group and one patient (7.7%) in the placebo group had ≥ 1 dose reduction and three patients (11.5%) in the nintedanib and none in the placebo group had ≥ 1 treatment interruption; three patients (11.5%) in the nintedanib group and none in the placebo group discontinued treatment (Figure 2). Mean (SD) exposure to trial medication over the whole trial was 46.4 (22.3) weeks for patients randomised to nintedanib and 49.6 (23.6) weeks for patients who received placebo followed by open-label nintedanib (Table S3).

Pharmacokinetics

The geometric mean (gMean) (gCV%) $AUC_{T,ss}$ for nintedanib was 175 ug*h/L (85.1) in patients aged 6 to 11 years and 160 ug*h/L (82.7) in patients aged 12 to 17 years. Additional pharmacokinetic data are shown in Table S4.

Adverse events

During the double-blind period, adverse events were reported in 22 patients (84.6%) in the nintedanib group and 11 patients (84.6%) in the placebo group (Table 4). Diarrhoea was the most frequent adverse event associated with nintedanib, reported in 10 patients (38.5%) in the nintedanib group and two patients (15.4%) in the placebo group. Two patients (7.7%) had adverse events that led to discontinuation of nintedanib (reported as epiphyses premature fusion [not confirmed by central review of imaging] and liver injury). Two patients (7.7%) in the nintedanib group and one patient (7.7%) in the placebo group had serious adverse events (see Table 4 for details).

Over the whole trial, adverse events were reported in all patients randomised to nintedanib and in 12 patients (92.3%) who received placebo as randomised treatment and then open-label nintedanib; serious adverse events were reported in five patients (19.2%) randomised to nintedanib and in three patients (23.1%) who received placebo followed by open-label nintedanib (See Table S5 for details). No patients had adverse events leading to treatment discontinuation during the open-label period. Two patients (7.7%) randomised to nintedanib had aspartate transaminase and/or alanine transaminase ≥ 3 times the upper limit of the normal range; none met criteria for Hy's law.

Epiphyseal growth plate and dental examinations

At week 24, 20 patients (76.9%) and nine patients (69.2%) in the nintedanib and placebo groups, respectively, had epiphyseal growth plate imaging. Pathological findings were observed in two patients (7.7%) in the nintedanib group and one patient (7.7%) in the placebo group (Table S6).

At week 24, dental examination was performed in 23 patients (88.5%) and 10 patients (76.9%), and dental imaging in 22 (84.6%) and 10 (76.9%) patients, in the nintedanib and placebo groups, respectively. On dental examination, new pathological findings were

reported in five patients (19.2%) treated with nintedanib and one patient (7.7%) who received placebo. On dental imaging, stunted growth of the dental root was reported in six patients (23.1%) treated with nintedanib and none who received placebo (Table S7). Review by the safety monitoring committee and a dental expert determined that in three patients, root development was completed (*i.e.* stunted growth was implausible) and in three patients, different angulations between assessments had led to an overread. Treatment was reinitiated in all cases. In five of the six patients, no indication of stunted growth of dental root was identified in central review of dental imaging at week 52. Details of these cases are provided in Table S8.

Height-for-age z-score

Adjusted mean (SE) changes from baseline in height-for-age z-score at week 24 were -0.05 (0.03) in the nintedanib group and -0.03 (0.04) in the placebo group (difference -0.02 [95% CI: $-0.12, 0.09$]; nominal $p=0.75$) (Figure S1).

Forced vital capacity

Adjusted mean (SE) changes from baseline in FVC % predicted at week 24 were 0.3 (1.3) in the nintedanib group and -0.9 (1.8) in the placebo group (difference 1.2 [95% CI: $-3.4, 5.8$]; nominal $p=0.60$) (Figure 3). The treatment effect of nintedanib observed in this trial was within the range of the effect observed in trials conducted in adults with fibrosing ILDs over 24 weeks (Figure S2).

SpO₂, 6MWT distance and PedsQL

Adjusted mean (SE) changes from baseline in SpO₂ at rest at week 24 were 0.07% (0.77) in the nintedanib group and -2.25% (1.08) in the placebo group (difference 2.31% [95% CI: $-0.39, 5.02$]; nominal $p=0.09$) (Figure 4). Adjusted mean (SE) changes from baseline in 6MWT distance at week 24 were 17.6 (16.5) m in the nintedanib group and 10.5 (22.9) m in the placebo group (difference 7.2 [95% CI: $-50.7, 65.0$]; nominal $p=0.80$) (Table S9).

Adjusted mean (SE) changes from baseline in the PedsQL patient report score at week 24 were 6.5 (1.9) and 5.5 (2.7) in the nintedanib and placebo groups, respectively (difference 1.0 [95% CI: -5.8, 7.9]; nominal p=0.76) (Table S8). Adjusted mean (SE) changes from baseline in the PedsQL parent report score at week 24 were 5.5 (2.5) and 5.6 (3.5) in the nintedanib and placebo groups, respectively (difference -0.1 [95% CI: -9.0, 8.7]; nominal p=0.98) (Table S10).

Discussion

The main objectives of the InPedILD trial were to determine the dosing of nintedanib that would result in an exposure in children and adolescents comparable to adults, and to assess the safety of nintedanib in children and adolescents with clinically significant fibrosing ILD. The results demonstrated that nintedanib had an acceptable safety profile in this patient population. As in adults [12–14,22], the most common adverse event associated with nintedanib in the InPedILD trial was diarrhoea, but the proportion of children who experienced diarrhoea was lower than that observed in adults, and there were no discontinuations due to diarrhoea during the double-blind period.

Inhibition of the vascular endothelial growth factor receptor (VEGFR) results in decreased angiogenesis, which is essential for bone growth and development [23]. Data from animal models have suggested that nintedanib, an inhibitor of VEGFR [24], may have reversible effects on the epiphyseal growth plates of large bones and an impact on tooth development [25]. Thus, close monitoring of growth, bone and tooth development was implemented in the InPedILD trial. Pathological findings on epiphyseal growth plate imaging showed no evidence of premature closure of the physes. Changes in height-for-age z-scores suggested normal linear growth. Although six cases of stunted dental root growth were reported, these could not be confirmed by an expert paediatric dentist taking into account additional clinical and demographic data. Although reassuring, the potential effects of nintedanib on

epiphyseal growth plates and dentition will continue to be monitored in the open-label extension study.

During the double-blind period of the InPedILD trial, five patients in the nintedanib group had COVID-19 compared with one patient in the placebo group. Three patients (11.5%) in the nintedanib group and four patients (30.8%) in the placebo group received a COVID-19 vaccine during the double-blind period; a further patient (7.7%) in the placebo group had COVID-19 before the trial. Based on mechanism of action, non-clinical and clinical data, there is no indication that nintedanib would increase the risk of infection or worsen the disease course of COVID-19.

A dose of 150 mg bid was investigated in the pivotal trials of nintedanib in adults with pulmonary fibrosis [12–14] and is the recommended dose for adult patients [26]. Studies investigating the impact of exposure on the efficacy and safety of nintedanib in adults support this dose [27,28]. In the InPedILD trial, dosing was based on weight-dependent allometric scaling. In adults treated with nintedanib 150 mg bid, the derived gMean (gCV%) $AUC_{T,ss}$ of nintedanib is 203 ug*h/L (67.5) and the median (5th, 95th percentile) $AUC_{T,ss}$ is 181 ug*h/L (81.5, 398) [Boehringer Ingelheim data on file]. Thus, the pharmacokinetic data from the InPedILD trial show that the weight-based dosing regimen achieved exposure in paediatric patients that was comparable to that observed in adults treated with 150 mg bid, supporting the use of this dosing regimen in the paediatric population.

FVC was an exploratory endpoint in the InPedILD trial. The mean change (SE) in FVC % predicted at week 24 was 0.3% (1.3) in the nintedanib group vs -0.9% (1.8) in the placebo group. We also observed a stabilisation of SpO₂ at rest over 24 weeks in the nintedanib group compared with a decline in the placebo group (mean [SE] changes of 0.07% [0.77] vs -2.25% [1.08]). These observations need to be interpreted with caution given the paucity of data on the natural history of lung function in children with ILD [7,29,30] and the short

duration of the trial. However, the observed reduction in decline in FVC % predicted with nintedanib versus placebo in this paediatric population was within the range observed in adults with fibrosing ILDs treated for 24 weeks.

Conducting clinical trials in children with fibrosing ILD is challenging due to factors including its rarity and a lack of consensus on how to measure the progression of pulmonary fibrosis in children [1]. Other than the InPedILD trial, the only randomised placebo-controlled trial of an intervention in children with fibrosing ILD to have published results is a trial of hydroxychloroquine conducted in Germany, which differed substantially from the InPedILD trial in its design [31]. The InPedILD trial is the first international placebo-controlled trial to have been conducted in children with ILD and as such represents a landmark in the field. However, it also has limitations, including the small sample size and short duration, which limit interpretation of the data. Of note, randomisation of 39 patients in the InPedILD trial required the involvement of dozens of sites, with a failure to meet radiological criteria based on central review the main reason for screen failure.

In conclusion, data from the InPedILD trial demonstrate that nintedanib has an acceptable safety and tolerability profile in children and adolescents with fibrosing ILD, with no new safety signals observed compared with adult patients. Exposure levels achieved with weight-based allometric dosing were within the range observed in adults. These data provide a scientific basis for the use of nintedanib in children and adolescents with fibrosing ILD.

Plain language summary

A plain language summary of these data is available here:

<https://www.globalmedcomms.com/respiratory/ERS2022/Deterding/plain-language-summary>

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Data sharing statement

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, BI grants all external authors access to relevant clinical study data. In adherence with the BI 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 journal, regulatory activities are

complete and other criteria are met. Researchers should use <https://vivli.org/> to request access and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

Table 1. Dosing and dose adjustments.

Weight bin	Weight range, kg	Dose, bid	Capsule strength	Reduced dose, bid	Capsule strength for reduced dose
1	13.5* to <23.0	50 mg	25 mg (2x)	25 mg	25 mg (1x)
2	23.0 to <33.5	75 mg	25 mg (3x)	50 mg	25 mg (2x)
3	33.5 to <57.5	100 mg	100 mg (1x) or 25 mg (4x)	75 mg	25 mg (3x)
4	≥57.5	150 mg	150 mg (1x) or 25 mg (6x)	100 mg	100 mg (1x) or 25 mg (4x)

*Patients with weight <13.5 kg were excluded from the trial.

Table 2. Baseline characteristics.

	Nintedanib (n=26)	Placebo (n=13)
Female, n (%)	16 (61.5)	8 (61.5)
Age, years, mean (SD)	12.5 (3.6)	12.9 (2.8)
Age categories, n (%)		
6 to <12 years	8 (30.8)	4 (30.8)
12 to <18 years	18 (69.2)	9 (69.2)
Height, cm, mean (SD)	147.0 (16.9)	148.4 (16.3)
Weight, kg, mean (SD)	40.9 (16.0)	44.7 (21.5)
Weight categories, n (%)		
≥13.5 to <23 kg	5 (19.2)	3 (23.1)
≥23 to <33.5 kg	2 (7.7)	3 (23.1)
≥33.5 to <57.5 kg	18 (69.2)	3 (23.1)
≥57.5 kg	1 (3.8)	4 (30.8)
Race, n (%)		
White	19 (73.1)	12 (92.3)
Black or African-American	3 (11.5)	0
Asian	2 (7.7)	0
Other/missing	2 (7.7)	1 (7.7)
Time since diagnosis of ILD, years, mean (SD)	5.0 (4.5)	7.1 (5.2)
Diagnosis, n (%)		
Surfactant protein deficiency	7 (26.9)	5 (38.5)
Systemic sclerosis	4 (15.4)	3 (23.1)
Toxic/radiation/drug-induced pneumonitis	3 (11.5)	1 (7.7)
Chronic hypersensitivity pneumonitis	2 (7.7)	0
Other (diagnoses made in one patient)	10 (38.5)	4 (30.8)
FVC, mL, mean (SD)	1633 (914)	1932 (991)
FVC % predicted, mean (SD)	57.7 (21.8)	62.9 (22.6)
FVC z-score*, mean (SD)	-3.6 (1.9)	-3.2 (1.9)
DLco % predicted [†] , mean (SD)	52.9 (26.7)	63.1 (10.7)

DLco, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease. *The z-score gives the number of standard deviations a certain value deviates from the mean value of a reference population. [†]Corrected for haemoglobin; n=18 in nintedanib group and n=9 in placebo group.

Table 3. Exposure to trial medication during double-blind period.

	Nintedanib (n=26)	Placebo (n=13)
Mean (SD) exposure, weeks	22.3 (4.8)	22.6 (4.2)
Median (min, max) exposure, weeks	23.9 (8.1, 28.6)	24.0 (9.4, 24.4)
Total dose*, g, mean (SD)	28.5 (10.9)	32.7 (14.8)

*For each patient, the total dose was the sum of durations of exposure to x g (days)*2* x g, where x was 0.025, 0.05, 0.075, 0.1, 0.15.

Table 4. Adverse events during double-blind period.

	Nintedanib (n=26)	Placebo (n=13)
Any adverse event(s)	22 (84.6)	11 (84.6)
Most frequent adverse event(s)*		
Diarrhoea	10 (38.5)	2 (15.4)
Vomiting	7 (26.9)	3 (23.1)
Dental caries	7 (26.9)	3 (23.1)
Nausea	5 (19.2)	3 (23.1)
Abdominal pain	5 (19.2)	3 (23.1)
COVID-19	5 (19.2)	1 (7.7)
Headache	3 (11.5)	1 (7.7)
Pyrexia	3 (11.5)	1 (7.7)
Rhinitis	3 (11.5)	0
Tooth impacted	2 (7.7)	2 (15.4)
Fatigue	2 (7.7)	2 (15.4)
Faeces soft	1 (3.8)	2 (15.4)
Oropharyngeal pain	1 (3.8)	2 (15.4)
Epistaxis	0	2 (15.4)
X-ray limb abnormal	0	2 (15.4)
Adverse event(s) leading to discontinuation	2 (7.7) [†]	0
Serious adverse event(s) [‡]	2 (7.7) [§]	1 (7.7)
Required or prolonged hospitalisation	2 (7.7)	0
Other medically important serious event	0	1 (7.7)
Fatal or life-threatening	0	0

Data are n (%) of patients with ≥1 such event. Adverse events with onset from the first intake of trial drug until the day prior to the first intake of open-label nintedanib or the last intake of randomised treatment plus 28 days (whichever occurred first) are shown. *Reported in >10% of patients in either treatment group based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). [†]Liver injury in one patient; epiphyses premature fusion in one patient. [‡]Defined as an adverse event that resulted in death, was life-threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason. [§]COVID-19 in one patient; respiratory distress and carbon dioxide increased in one patient. ^{||}Frontal lobe epilepsy.

FIGURE LEGENDS

Figure 1. Trial design

Figure 2. Disposition of patients during double-blind period.

Figure 3. Change in FVC % predicted over 24 weeks.

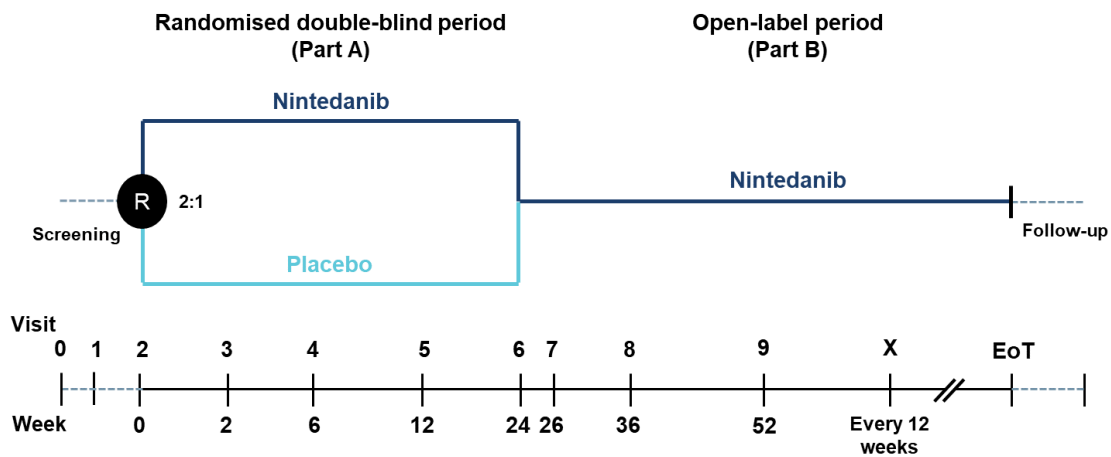
Figure 4. Change in SpO₂ at rest over 24 weeks.

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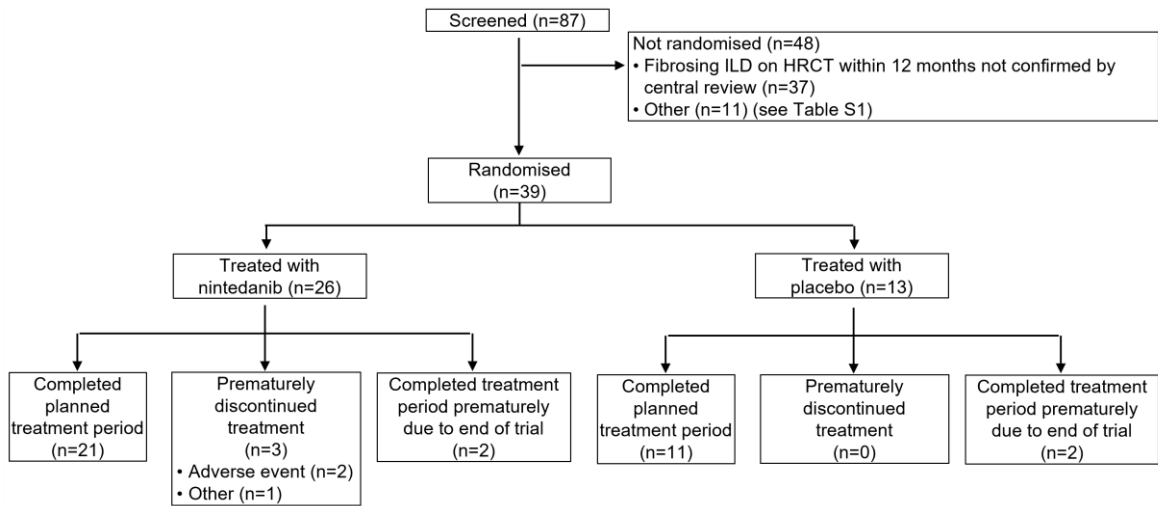
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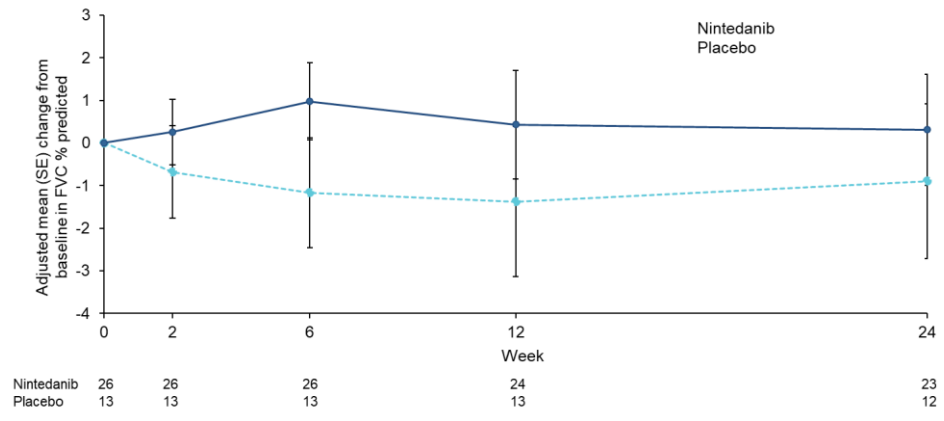
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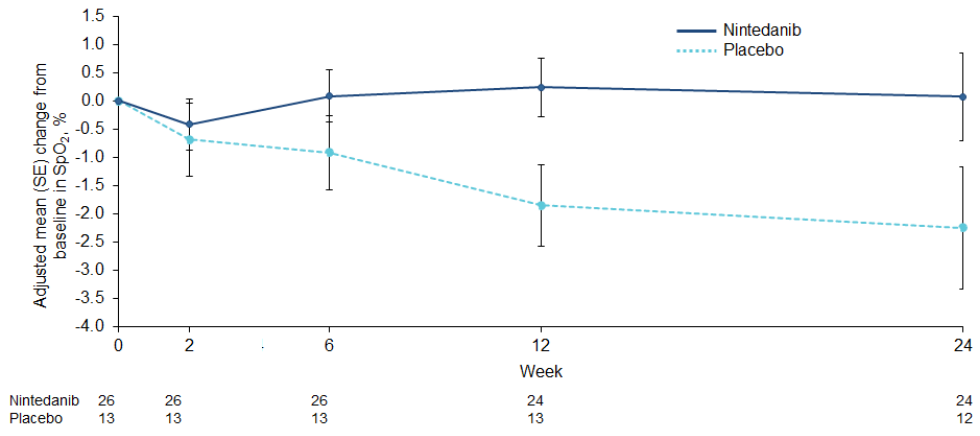
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EoT, end of treatment.







Supplementary Material

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Determination of fibrosing ILD

Any of the following lung biopsy findings were accepted if confirmed by central review:

- Non-specific interstitial pneumonia (fibrosing)
- Usual interstitial pneumonia
- Honeycomb lung
- Interstitial fibrosis on a significant component of the lung
- Lobular remodelling on a significant component of the lung

For patients with pathological findings of fibrosis on lung biopsy, fibrosis was confirmed if ≥ 1 of the following criteria was met on a HRCT scan performed ≤ 12 months before screening, confirmed by central review:

- Reticular abnormality
- Traction bronchiectasis
- Architectural distortion
- Honeycombing

Co-existing cystic abnormalities or ground glass opacity were acceptable. Co-existing multifocal non-fibrotic, non-dependent consolidations (e.g., organising pneumonia, infection) were not allowed.

For patients without a lung biopsy, or whose biopsy results did not meet the criteria for fibrosis, ≥ 2 of the following findings were required on ≥ 2 HRCT scans (with the most recent performed ≤ 12 months before screening):

- Reticular abnormality
- Traction bronchiectasis
- Architectural distortion with/without ground glass opacification
- Honeycombing
- Cystic abnormalities

Key exclusion criteria

Patients were excluded if they had aspartate transaminase, alanine transaminase, or total bilirubin >1.5 times the upper limit or normal; creatinine clearance (based on Schwartz formula) <30 mL/min; chronic liver disease (Child-Pugh A, B or C); or weight <13.5 kg at screening. Patients were excluded if their life expectancy for any disease other than ILD was <2.5 years (based on investigator assessment), if they were diagnosed a growth disorder, such as growth hormone deficiency or a genetic disorder associated with short stature, and/or were receiving growth hormone therapy ≤ 6 months before randomisation. Patients with bleeding risk (defined as genetic predisposition to bleeding; requirement for fibrinolysis, full-dose therapeutic anticoagulation or high-dose antiplatelet therapy; history of

haemorrhagic central nervous system event in the prior 12 months; haemoptysis or haematuria, active gastrointestinal bleeding or gastrointestinal ulcers, or major injury or surgery in the prior 3 months; or international normalised ratio >2 , prolongation of prothrombin time by >1.5 times the upper limit of normal, or prolongation of activated partial thromboplastin time by >1.5 times the upper limit of normal) at screening were excluded. Patients with significant pulmonary arterial hypertension (PAH) (defined as previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterisation showing a cardiac index ≤ 2 l/min/m², or parenteral therapy with epoprostenol or treprostinil for PAH) were excluded. Patients with severe uncontrolled hypertension (children 6 to ≤ 12 years old: ≥ 95 th percentile + 12 mmHg or $\geq 140/90$ mmHg, whichever was lower [systolic or diastolic blood pressure equal to or greater than the calculated target value]; adolescents 13 to 17 years old: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) in prior ≤ 6 months, myocardial infarction in prior ≤ 6 months, unstable cardiac angina in prior ≤ 6 months, or thrombotic event (including stroke and transient ischemic attack) in prior ≤ 12 months were excluded. Treatment with nintedanib or another investigational therapy within 1 month or 5 half-lives (whichever was shorter but ≥ 1 week) before randomisation was not permitted. Female patients of childbearing potential were required to confirm that sexual abstinence was standard practice and was to be continued until 3 months after their last drug intake or that they would use a highly effective method of birth control in combination with a barrier method from 28 days prior to 3 months after the last intake of study drug.

Table S1. Reason for non-randomisation.

	n (%)
COVID-19 related	3 (3.4)
Inclusion criteria not met*	41 (47.1)
Evidence of fibrosing ILD on HRCT within 12 months of visit 1 as assessed by the investigator and confirmed by central review	37 (42.5)
Clinically significant disease at visit 2, as assessed by the investigator based on Fan score ≥ 3 or documented evidence of clinical progression	3 (3.4)
FVC % predicted $\geq 25\%$ at visit 2	2 (2.3)
6 to 17 years old at visit 2	1 (1.1)
Exclusion criteria met*	5 (5.7)
AST and/or ALT $> 1.5 \times$ upper limit of normal at visit 1	3 (3.4)
Significant pulmonary arterial hypertension	1 (1.1)
Patient not able or willing to adhere to trial procedures	1 (1.1)

Data are n (% of screened patients). *A patient may have been counted in ≥ 1 category. ALT, alanine transaminase. AST, aspartate transaminase.

Table S2. Criteria for clinically significant disease.

	Nintedanib (n=26)	Placebo (n=13)
Fan score ≥ 3	17 (65.4)	6 (46.2)
Clinical progression*		
Relative decline in FVC $\geq 10\%$ predicted	5 (19.2)	3 (23.1)
Relative decline in FVC of 5–10% predicted with worsening symptoms	6 (23.1)	3 (23.1)
Worsening fibrosis on HRCT	14 (53.8)	11 (84.6)
Other measures of clinical worsening attributed to progressive pulmonary fibrosis	9 (34.6)	3 (23.1)

Data are n (%) of patients. *A patient may have been counted in ≥ 1 category.

Table S3. Exposure to trial medication over whole trial.

	Nintedanib (n=26)	Placebo/nintedanib* (n=13)
Mean (SD) exposure, weeks	46.4 (22.3)	49.6 (23.6)
Median (min, max) exposure, weeks	51.5 (8.1, 85.1)	51.9 (9.4, 88.6)
Total dose [†] , g, mean (SD)	58.5 (36.8)	69.0 (36.1)

*Patients received placebo (blinded) for 24 weeks followed by nintedanib (open-label). [†]For each patient, the total dose was the sum of durations of exposure to x g (days)*2* x g, where x was 0.025, 0.05, 0.075, 0.1, 0.15.

Table S4. Pharmacokinetic parameters of nintedanib.

	Age 6 to 11 years (n=10)	Age 12 to 17 years (n=22)
AUC _{T,ss} (ng·h/mL)	175 (85.1)	160 (82.7)
C _{max,ss} (ng/mL)	28.7 (85.1)	33.0 (90.7)*
t _{max,ss} (h)	2.00 (0.92, 4.17)	2.67 (0.92, 5.75)*
t _{½,ss} (h)	5.37 (80.9)	3.87 (43.3)
CL/F _{ss} (mL/min)	6800 (60)	10800 (78)
V _z /F _{ss} (L)	3160 (89)	3600 (113)

Data are geometric mean (geometric coefficient of variation) except for t_{max}, which are median and range (minimum, maximum). Based on pooled data at weeks 2 and 26 and non-compartmental analysis.

*n=25.

AUC_{T,ss}; area under the plasma concentration–time curve at steady state; C_{max,ss}; maximum measured concentration in plasma at steady state; t_{max,ss}; time from dosing to maximum measured concentration in plasma at steady state; t_{½,ss}; terminal half-life in plasma at steady state; CL/F_{ss}; apparent clearance in the plasma at steady-state following extravascular multiple dose administration; V_z/F_{ss}; apparent volume of distribution during the terminal phase λ_z at steady state following extravascular administration.

Table S5. Adverse events over the whole trial.

	Nintedanib (n=26)	Placebo/nintedanib* (n=13)
Any adverse event(s)	26 (100)	12 (92.3)
Most frequent adverse event(s) [†]		
Diarrhoea	12 (46.2)	7 (53.8)
COVID-19	9 (34.6)	2 (15.4)
Vomiting	7 (26.9)	5 (38.5)
Dental caries	7 (26.9)	4 (30.8)
Tooth development disorder	7 (26.9)	1 (7.7)
Nausea	6 (23.1)	8 (61.5)
Abdominal pain	6 (23.1)	5 (38.5)
Pyrexia	4 (15.4)	2 (15.4)
Rhinitis	4 (15.4)	0
Headache	3 (11.5)	3 (23.1)
Abdominal pain upper	3 (11.5)	1 (7.7)
Malpositioned teeth	3 (11.5)	1 (7.7)
Chest pain	2 (7.7)	2 (15.4)
Tooth impacted	2 (7.7)	2 (15.4)
Fatigue	2 (7.7)	2 (15.4)
Nasopharyngitis	1 (3.8)	3 (23.1)
Oropharyngeal pain	1 (3.8)	3 (23.1)
SARS-CoV-2 test positive	1 (3.8)	2 (15.4)
Faeces soft	1 (3.8)	2 (15.4)
Pain in extremity	1 (3.8)	2 (15.4)
Epistaxis	0	4 (30.8)
Cough	0	3 (23.1)
X-ray limb abnormal	0	2 (15.4)
Adverse event(s) leading to discontinuation	2 (7.7)	0
Serious adverse events [†]	5 (19.2)	3 (23.1)
Required or prolonged hospitalisation	3 (11.5)	0
Other medically important serious event	2 (7.7)	3 (23.1)
Fatal or life-threatening	0	0

Data are n (%) of patients with ≥ 1 such event. Adverse events were reported over the whole trial including a 28-day post-treatment period. *Patients received placebo (blinded) for 24 weeks followed by nintedanib (open-label). †Reported in >10% of patients in either treatment group based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). ‡Adverse event that resulted in death, was life-threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason. In patients randomised to nintedanib, the serious adverse events were COVID-19 (n=2); respiratory distress (n=1); interstitial lung disease (n=1); carbon dioxide increased (n=1); tooth development disorder (n=1); and liver injury (n=1). In patients who received placebo then open-label nintedanib, the serious adverse events were drug-induced liver injury (n=1); frontal lobe epilepsy (n=1); and neurogenic shock (n=1).

Table S6. Pathological findings of epiphyseal growth plate on imaging at week 24.

	Nintedanib (n=26)	Placebo (n=13)
Patients with epiphyseal growth plate imaging	20 (76.9)	9 (69.2)
≥1 pathological finding of epiphyseal growth	2 (7.7)	1 (7.7)
Pathological findings at distal femur	2 (7.7)	0
Metaphyseal lines	1 (3.8)	0
Other	1 (3.8)	0
Pathological findings at proximal tibia	1 (3.8)	1 (7.7)
Narrowing of lucent growth plate margin	0	1 (7.7)
Other	1 (3.8)	0

Data are n (%).

Table S7. Pathological findings on dental examination and imaging at week 24.

	Nintedanib (n=26)	Placebo (n=13)
Patients with dental examination	23 (88.5)	10 (76.9)
Pathological findings*	5 (19.2)	1 (7.7)
New pathological findings	5 (19.2)	1 (7.7)
Patients with dental imaging	22 (84.6)	10 (76.9)
Stunted growth of dental root [†]	6 (23.1)	0
Impacted permanent teeth	4 (15.4)	2 (15.4)
Pre-defined additional findings [‡]	5 (19.2)	1 (7.7)
Other additional findings	1 (3.8)	2 (15.4)

Data are n (%). *Included findings that showed worsening compared with the baseline finding. [†]e.g., premature closing of the apex/apices with a blunted root appearance. [‡]Cyst, abscess, solid lesion or bone abnormality.

Table S8. Summary of cases with stunted growth of the dental root.

Age, sex	Baseline findings on dental imaging	Teeth with stunted growth on follow-up	Dental exam*	Comment
14 years, F	Short root: 41 and 31 (acquired enamel hypoplasia); hyperdontia; tooth development disorder: 34 and 44 ectopic; impacted permanent teeth: 43, 47, 33, 37, 38, 48,14, 26 and 27	31, 41	Visits 5, 6, 8 and 9: no new pathological findings	Root completed for 31 and 41 (at ~9 years)
16 years, F	Short root: 11, 31 and 41; abscess: 37	11	Visit 2: dental caries 14, 16, 17, 25, 26, 27, 34, 35, 36, 37, 45 and 47; tooth abscess 37, Visit 5: extraction 14, 25, 47 Visits 6 and 8: new dental caries 13 and 44	Root completed for 11 (at ~10 years)
12 years, F	Short root: 11 and 21; impacted permanent teeth: 15, 25 and 35	15, 24, 47 [†]	Visit 2: dental caries 46 Visits 5, 6 and 8: no new pathological findings	Root completed for 15 (at ~13–14 years); root completed for 24 (at ~12–13 years); root completed for 47 (at ~14–15 years)
6 years, F	Impacted permanent teeth: 37	11, 12, 13, 21, 22, 23, 31, 32, 41, 42; at visit 9:	Visits 5, 6, 8 and 9: no new pathological findings	Root completed for 31, 32, 41, 42 (at ~9– years)

		stunted growth reported for 31, 32, 41, 42		
15 years, F	None	24, 25	Visits 5, 6 and 8: no new pathological findings	Root completed for 24 and 25 (at ~12–14 years)
13 years, F	Short root: 11 and 21; impacted permanent teeth: 47, 17, 27	17 [‡]	Visits 5, 6 and 8: no new pathological findings	Root completed for 17 (at ~14–16 years)

*Visit 2: baseline; Visit 5: week 12; Visit 6: week 24; Visit 8: week 36; Visit 9: week 52. [†]Malpositioned teeth (abnormal position of dental roots in x-ray) was reported 1 week after visit 6. [‡]Impacted permanent teeth (13) was reported at visit 6.

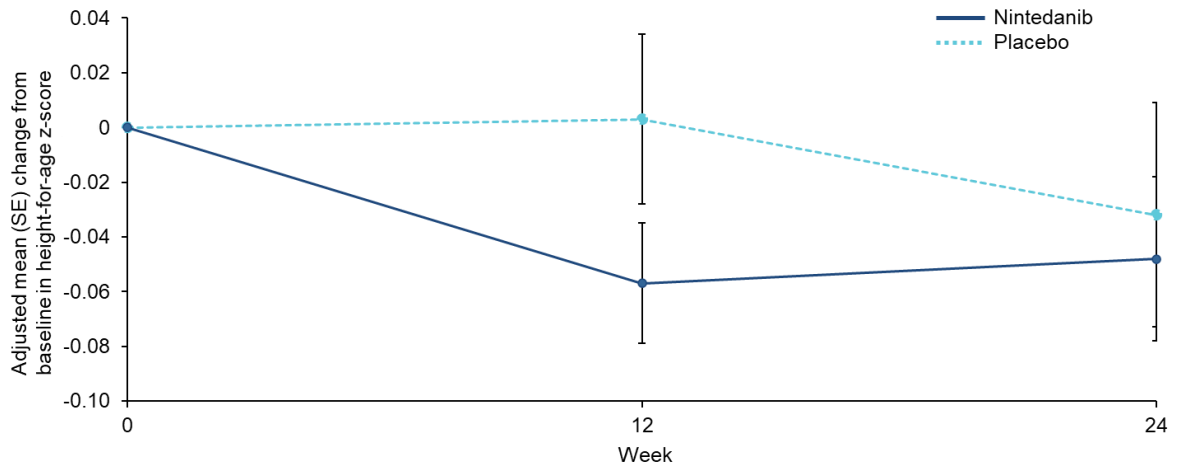
Table S9. Change from baseline in 6-minute walk test (6MWT) distance at week 24.

	Nintedanib (n=26)	Placebo (n=13)
Mean (SD) 6MWT distance at baseline, m	389.6 (134.4)	370.8 (135.7)
Adjusted mean (SE) change from baseline in 6MWT distance at week 24, m	17.6 (16.5)	10.5 (22.9)
Adjusted mean difference (95% CI)	7.2 (-50.7, 65.0)	
Nominal p-value	0.80	

Table S10. Change from baseline in Pediatric Quality of Life (PedsQL) questionnaire scores at week 24.

	Nintedanib (n=26)	Placebo (n=13)
Patient report		
Mean (SD) patient report score at baseline	66.9 (14.1)	71.6 (14.4)
Adjusted mean (SE) change from baseline in patient report score at week 24	6.5 (1.9)	5.5 (2.7)
Adjusted mean difference (95% CI)	1.0 (-5.8, 7.9)	
Nominal p-value	0.76	
Parent report		
Mean (SD) parent report score at baseline	60.4 (19.1)	64.7 (20.6)
Adjusted mean (SE) change from baseline in parent report score at week 24	5.5 (2.5)	5.6 (3.5)
Adjusted mean difference (95% CI)	-0.1 (-9.0, 8.7)	
Nominal p-value	0.98	

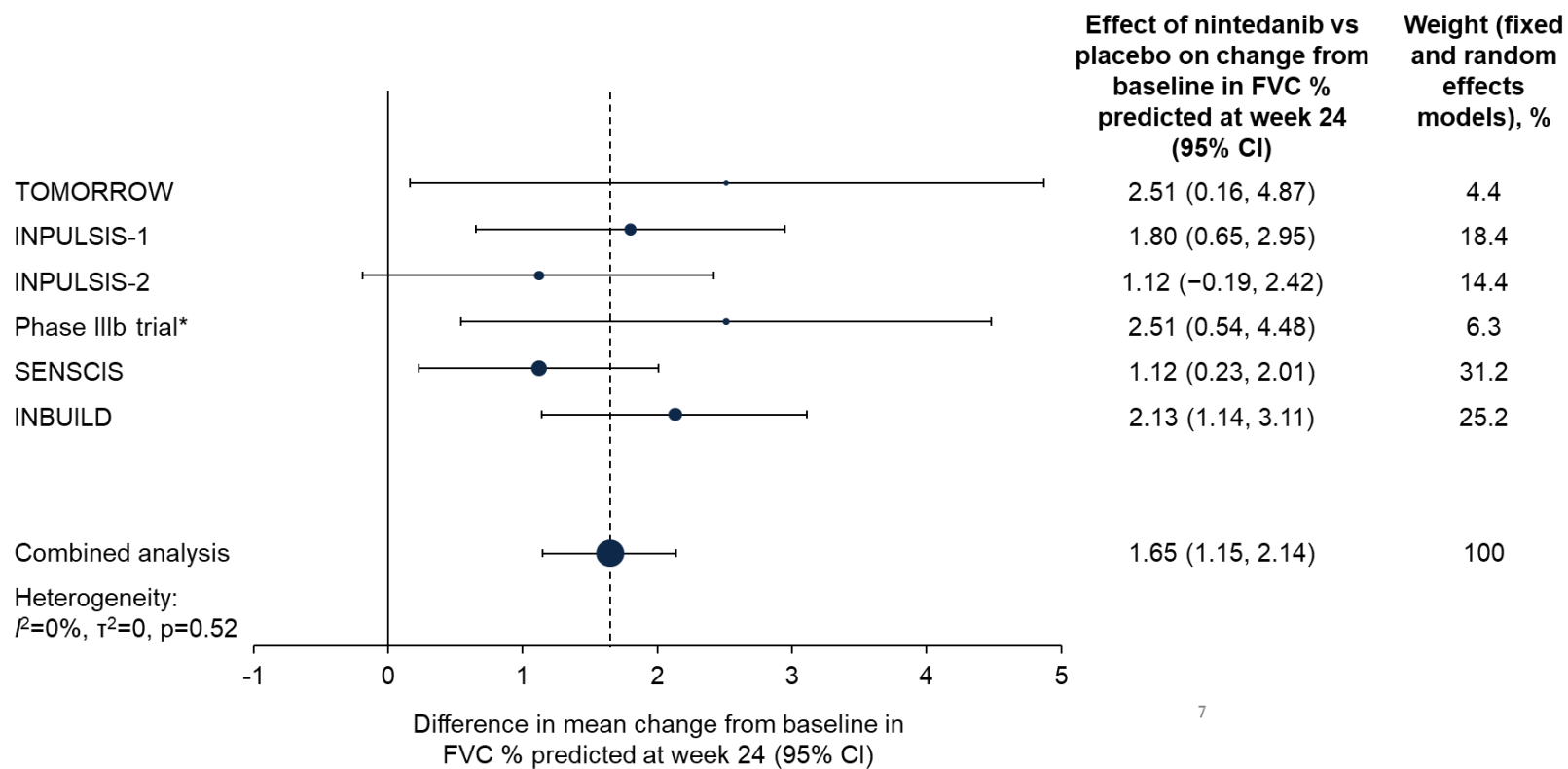
Figure S1. Change in height-for-age z-score over 24 weeks.



Nintedanib	26	25	22
Placebo	13	13	12

The z-score gives the number of standard deviations a certain value deviates from the mean value of the reference population. Mean (SD) height-for-age z-score at baseline was -0.76 (1.29) in the nintedanib group and -1.15 (1.37) in the placebo group.

Figure S2. Meta-analysis of change from baseline in FVC % predicted at week 24 in adult patients with fibrosing ILDs.



*clinicaltrials.gov, NCT01979952.