Nintedanib in children and adolescents with fibrosing interstitial lung diseases

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Abstract

Background Childhood interstitial lung disease (ILD) 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.

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

Results 26 patients received nintedanib and 13 patients received placebo. The geometric mean (geometric coefficient of variation) $AUC_{\tau,ss}$ for nintedanib was 175 $\mu g \cdot h \cdot L^{-1}$ (85.1%) in patients aged 6–11 years and 160 $\mu g \cdot h \cdot L^{-1}$ (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 percentage predicted forced vital capacity at week 24 were 0.3±1.3% in the nintedanib group and −0.9±1.8% in the placebo group.

Conclusions 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, 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; EU Clinical Trials Register: EudraCT 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 end-points were collected to support evaluation of the benefit–risk of nintedanib in the paediatric population.

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 (supplementary material), FVC ⩾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 ⩾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 or 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 and 12–17 years) (figure 1). Dosing was based on

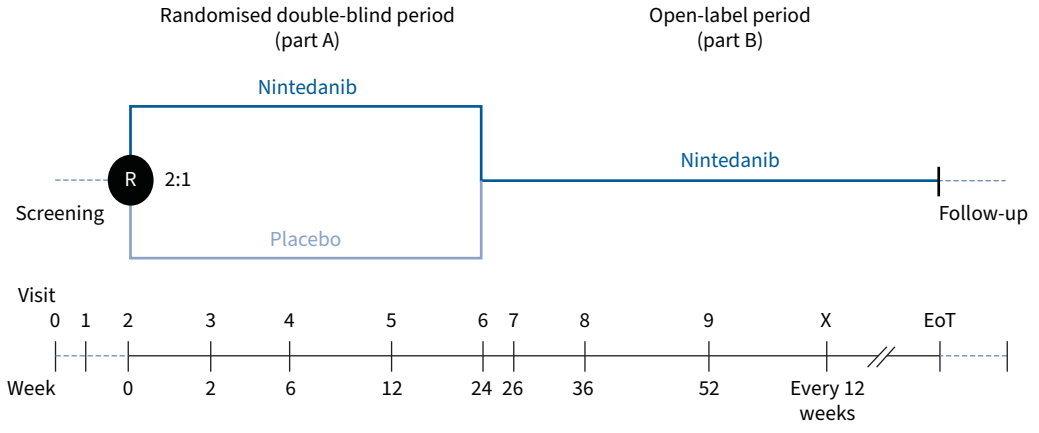

FIGURE 1 Trial design. R: randomisation; EoT: end of treatment.

weight-dependent allometric scaling. Starting doses were 50, 75, 100 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 the trial drug or within 8 weeks for adverse events not considered related to the 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 the 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; EU Clinical Trials Register: EudraCT 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 to 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 categorised 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.

End-points

The co-primary end-points were the area under the plasma concentration–time curve at steady state ($AUC_{\tau,ss}$) 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 the 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). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 25 (www.meddra.org).

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 end-points included the proportion of patients with pathological findings of epiphyseal growth plates 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 end-point.

Secondary efficacy end-points included changes in FVC % pred, peripheral oxygen saturation (S_{pO_2}) at rest, 6-min walk test (6MWT) distance and Pediatric Quality of Life (PedsQL) questionnaire scores at

TABLE 1 Dosing and dose adjustments

Weight bin	Weight range, kg	Dose, mg twice daily	Capsule strength, mg	Reduced dose, mg twice daily	Capsule strength for reduced dose, mg
1	13.5[#]– <23.0	50	25 (2×)	25	25 (1×)
2	23.0– <33.5	75	25 (3×)	50	25 (2×)
3	33.5– <57.5	100	100 (1×) or 25 (4×)	75	25 (3×)
4	⩾57.5	150	150 (1×) or 25 (6×)	100	100 (1×) or 25 (4×)

[#]: patients with weight <13.5 kg were excluded from the trial.

week 24. Spirometry was performed using standardised spirometers supplied to each site and according to American Thoracic Society/European Respiratory Society guidelines [18]. FVC % pred values were calculated using equations published by the 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, $AUC_{\tau,ss}$ was calculated using noncompartmental and compartmental analyses and descriptive statistics. In patients randomised to nintedanib, the $AUC_{\tau,ss}$ at week 2 was used; if this value was missing, the value at week 26 was used. In patients randomised to placebo, the $AUC_{\tau,ss}$ at week 26 (corresponding to week 2 of nintedanib treatment) was used. Pharmacokinetic analyses were conducted in patients who received ⩾1 doses of trial medication and provided evaluable data for ⩾1 pharmacokinetic end-points without protocol violations relevant to the evaluation of pharmacokinetics. Safety analyses were conducted in patients who received ⩾1 doses of trial medication. Adjusted mean changes from baseline in FVC % pred, S_{pO_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 end-point 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 (gCV) 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 and 12–17 years) would be needed to achieve ⩾80% probability (loosely referred to as power [21]) of having the 95% confidence interval of CL/F_{ss} and $AUC_{\tau,ss}$ 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 and ⩾20 aged 12–17 years) was targeted.

Results

Patients

Of 87 patients screened, 39 patients (12 patients aged 6–11 years and 27 patients aged 12–17 years) were randomised and treated (26 patients with nintedanib and 13 patients with placebo) (figure 2 and supplementary table S1). Baseline characteristics were generally balanced between the treatment groups (table 2). The majority of patients were female (61.5%) and White race (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%) (supplementary 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 reductions and three patients (11.5%) in the nintedanib and none in the placebo group had ⩾1 treatment interruptions; 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 (supplementary table S3).

Pharmacokinetics

The geometric mean (gCV) $AUC_{\tau,ss}$ for nintedanib was 175 $\mu g \cdot h \cdot L^{-1}$ (85.1%) in patients aged 6–11 years and 160 $\mu g \cdot h \cdot L^{-1}$ (82.7%) in patients aged 12–17 years. Additional pharmacokinetic data are shown in supplementary 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

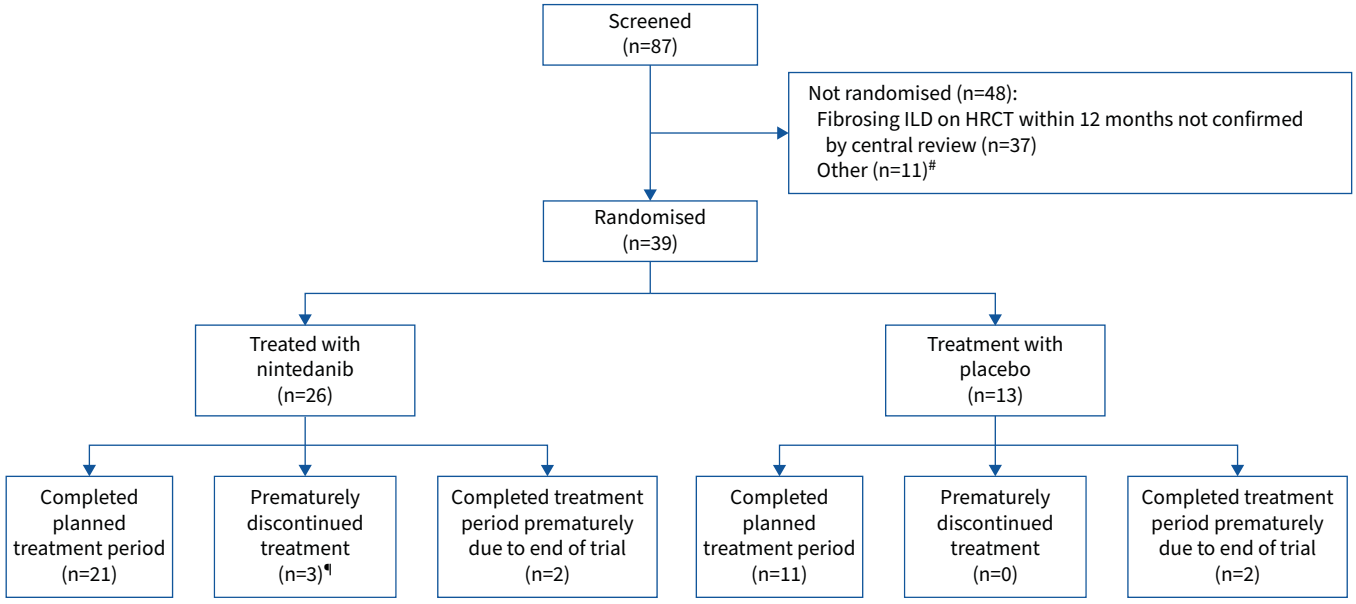

FIGURE 2 Disposition of patients during the double-blind period. #: see supplementary table S1; ¶: adverse event (n=2) and other (n=1). ILD: interstitial lung disease; HRCT: high-resolution computed tomography.

TABLE 2 Baseline characteristics

	Nintedanib (n=26)	Placebo (n=13)
Female	16 (61.5)	8 (61.5)
Age, years	12.5±3.6	12.9±2.8
Age categories		
6– <12 years	8 (30.8)	4 (30.8)
12– <18 years	18 (69.2)	9 (69.2)
Height, cm	147.0±16.9	148.4±16.3
Weight, kg	40.9±16.0	44.7±21.5
Weight categories		
13.5– <23 kg	5 (19.2)	3 (23.1)
23– <33.5 kg	2 (7.7)	3 (23.1)
33.5– <57.5 kg	18 (69.2)	3 (23.1)
57.5 kg	1 (3.8)	4 (30.8)
Race		
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	5.0±4.5	7.1±5.2
Diagnosis		
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	1633±914	1932±991
FVC % pred	57.7±21.8	62.9±22.6
FVC z-score#	−3.6±1.9	−3.2±1.9
D_{LCO} % pred¶	52.9±26.7	63.1±10.7

Data are presented as n (%) or mean±SD. ILD: interstitial lung disease; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. #: 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 the nintedanib group and n=9 in the placebo group).

TABLE 3 Exposure to trial medication during the double-blind period

	Nintedanib (n=26)	Placebo (n=13)
Mean±SD exposure, weeks	22.3±4.8	22.6±4.2
Median (minimum–maximum) exposure, weeks	23.9 (8.1–28.6)	24.0 (9.4–24.4)
Mean±SD total dose[#], g	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 and 0.15.

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 (table 4).

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 (supplementary table S5). 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.

TABLE 4 Adverse events during the 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)
Radiography 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)[f]
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 presented as n (%) of patients with ⩾1 such events. Adverse events with onset from the first intake of the 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; [¶]: liver injury in one patient, and 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, and respiratory distress and carbon dioxide increased in one patient; [f]: frontal lobe epilepsy.

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 (supplementary table S6).

At week 24, dental examination was performed in 23 patients (88.5%) and 10 patients (76.9%), and dental imaging in 22 patients (84.6%) and 10 patients (76.9%), 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 (supplementary 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 supplementary 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) (supplementary figure S1).

Forced vital capacity

Adjusted mean±SE changes from baseline in FVC % pred 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 (supplementary figure S2).

S_{pO_2}, 6MWT distance and PedsQL questionnaire

Adjusted mean±SE changes from baseline in S_{pO_2} 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) m; nominal p=0.80) (supplementary 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) (supplementary 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) (supplementary table S10).

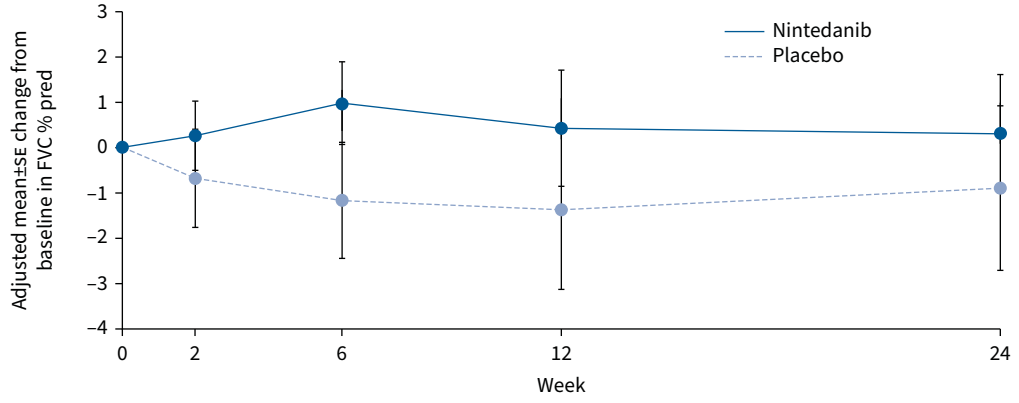

FIGURE 3 Change in percentage predicted forced vital capacity (FVC) over 24 weeks.

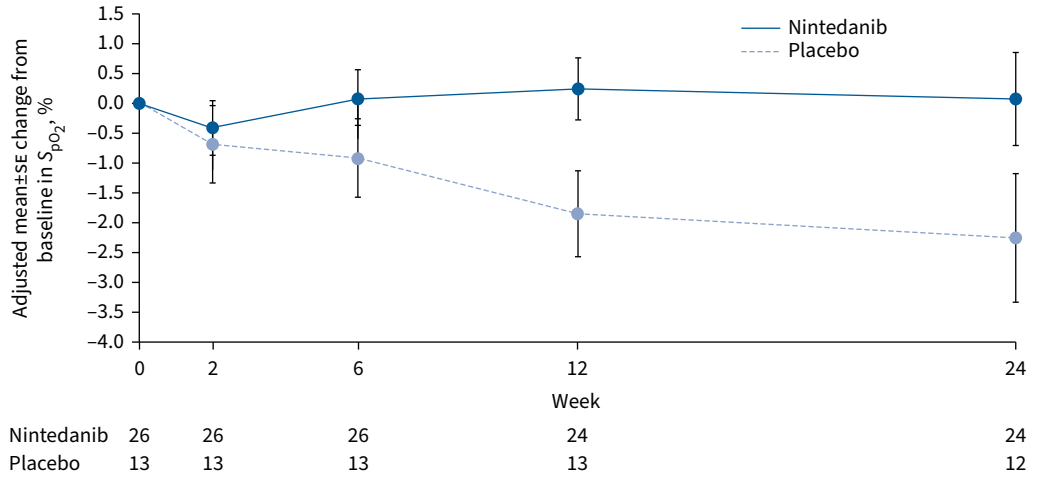

FIGURE 4 Change in peripheral oxygen saturation (S_{pO_2}) at rest over 24 weeks.

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 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 InPedILD-ON open-label extension study.

During the double-blind period of the InPedILD trial, five patients in the nintedanib group had coronavirus disease 2019 (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, nonclinical 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 twice daily 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 twice daily, the derived geometric mean (gCV) $AUC_{\tau,ss}$ of nintedanib is 203 µg·h·L^{-1} (67.5%) and the median (5th–95th percentile) $AUC_{\tau,ss}$ is 181 (81.5–398) µg·h·L^{-1} (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 twice daily, supporting the use of this dosing regimen in the paediatric population.

FVC was an exploratory end-point in the InPedILD trial. The mean±SE change in FVC % pred at week 24 was 0.3±1.3% in the nintedanib group *versus* −0.9±1.8% in the placebo group. We also observed a stabilisation of S_{pO_2} at rest over 24 weeks in the nintedanib group compared with a decline in the placebo

group (mean±SE change 0.07±0.77% *versus* −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 % pred 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 had 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.

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A plain language summary of these data is available from www.globalmedcomms.com/respiratory/ERS2022/Deterding/plain-language-summary

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References

1 Deterding RR, DeBoer EM, Cidon MJ, *et al.* Approaching clinical trials in childhood interstitial lung disease and pediatric pulmonary fibrosis. *Am J Respir Crit Care Med* 2019; 200: 1219–1227.
2 Griese M. Etiologic classification of diffuse parenchymal (interstitial) lung diseases. *J Clin Med* 2022; 11: 1747.
3 Hartl D, Griese M. Interstitial lung disease in children – genetic background and associated phenotypes. *Respir Res* 2005; 6: 32.
4 Glasser SW, Hardie WD, Hagood JS. Pathogenesis of interstitial lung disease in children and adults. *Pediatr Allergy Immunol Pulmonol* 2010; 23: 9–14.
5 Cidon M, Bansal M, Hartl D. Pulmonary manifestations of rheumatologic diseases. *Curr Opin Pediatr* 2017; 29: 311–319.
6 Cunningham S, Jaffe A, Young LR. Children's interstitial and diffuse lung disease. *Lancet Child Adolesc Health* 2019; 3: 568–577.
7 Nathan N, Thouvenin G, Fauroux B, *et al.* Interstitial lung disease: physiopathology in the context of lung growth. *Paediatr Respir Rev* 2011; 12: 216–222.
8 Bush A, Cunningham S, de Blic J, *et al.* European protocols for the diagnosis and initial treatment of interstitial lung disease in children. *Thorax* 2015; 70: 1078–1084.
9 Wollin L, Wex E, Pautsch A, *et al.* Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015; 45: 1434–1445.
10 Wollin L, Distler JHW, Redente EF, *et al.* Potential of nintedanib in treatment of progressive fibrosing interstitial lung diseases. *Eur Respir J* 2019; 54: 1900161.
11 Paterniti MO, Bi Y, Rekić D, *et al.* Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2017; 14: 1395–1402.
12 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
13 Distler O, Highland KB, Gahlemann M, *et al.* Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518–2528.
14 Flaherty KR, Wells AU, Cottin V, *et al.* Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.
15 Bonella F, Cottin V, Valenzuela C, *et al.* Meta-analysis of effect of nintedanib on reducing FVC decline across interstitial lung diseases. *Adv Ther* 2022; 39: 3392–3402.
16 Deterding R, Griese M, Deutsch G, *et al.* Study design of a randomised, placebo-controlled trial of nintedanib in children and adolescents with fibrosing interstitial lung disease. *ERJ Open Res* 2021; 7: 00805-2020.
17 Fan LL, Kozinetz CA. Factors influencing survival in children with chronic interstitial lung disease. *Am J Respir Crit Care Med* 1997; 156: 939–942.
18 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
19 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
20 Niemitz M, Schwerk N, Goldbeck L, *et al.* Development and validation of a health-related quality of life questionnaire for pediatric patients with interstitial lung disease. *Pediatr Pulmonol* 2018; 53: 954–963.
21 Wang Y, Jadhav PR, Lala M, *et al.* Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. *J Clin Pharmacol* 2012; 52: 1601–1606.
22 Lancaster L, Crestani B, Hernandez P, *et al.* Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. *BMJ Open Respir Res* 2019; 6: e000397.
23 Hu K, Olsen BR. The roles of vascular endothelial growth factor in bone repair and regeneration. *Bone* 2016; 91: 30–38.

24 Hilberg F, Roth GJ, Krssak M, *et al.* BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res* 2008; 68: 4774–4782.

25 Food and Drug Administration. OFEV (nintedanib) pharmacology/toxicology NDA/BLA review and evaluation. 2014. www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205832Orig1s000PharmR.pdf Date last accessed: 23 June 2022.

26 Boehringer Ingelheim International GmbH. OFEV (nintedanib) prescribing information. 2022. https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Ofev/ofev.pdf Date last accessed: 23 June 2022.

27 Schmid U, Weber B, Magnusson MO, *et al.* Exposure-efficacy analyses of nintedanib in patients with chronic fibrosing interstitial lung disease. *Respir Med* 2021; 180: 106369.

28 Schmid U, Weber B, Sarr C, *et al.* Exposure–safety analyses of nintedanib in patients with chronic fibrosing interstitial lung disease. *BMC Pulm Med* 2021; 21: 244.

29 Ring AM, Carlens J, Bush A, *et al.* Pulmonary function testing in children's interstitial lung disease. *Eur Respir Rev* 2020; 29: 200019.

30 DeBoer EM, Liptzin DR, Humphries SM, *et al.* Ground glass and fibrotic change in children with surfactant protein C dysfunction mutations. *Pediatr Pulmonol* 2021; 56: 2223–2231.

31 Griese M, Kappler M, Stehling F, *et al.* Randomized controlled phase 2 trial of hydroxychloroquine in childhood interstitial lung disease. *Orphanet J Rare Dis* 2022; 17: 289.