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: ≥95th percentile + 12 mmHg or ≥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 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 ≥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 × 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 ≥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=23)
$AUC_{\tau,ss}$ (ng·h/mL)	175 (85.1)	167 (83.6)
$C_{max,ss}$ (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)	3.82 (42.7)
CL/F_{ss} (mL/min)	6800 (60)	10300 (80)
V_z/F_{ss} (L)	3160 (89)	3420 (115)

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.

$AUC_{\tau,ss}$; 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 λz 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.

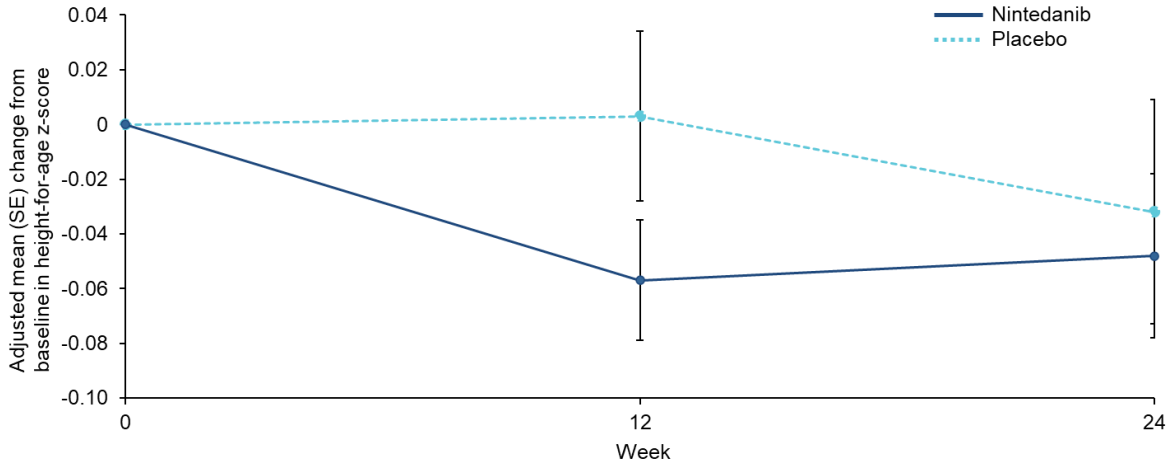
Table S9. Change from baseline in 6-minute walk test (6MWT) distance at week 24.

	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	

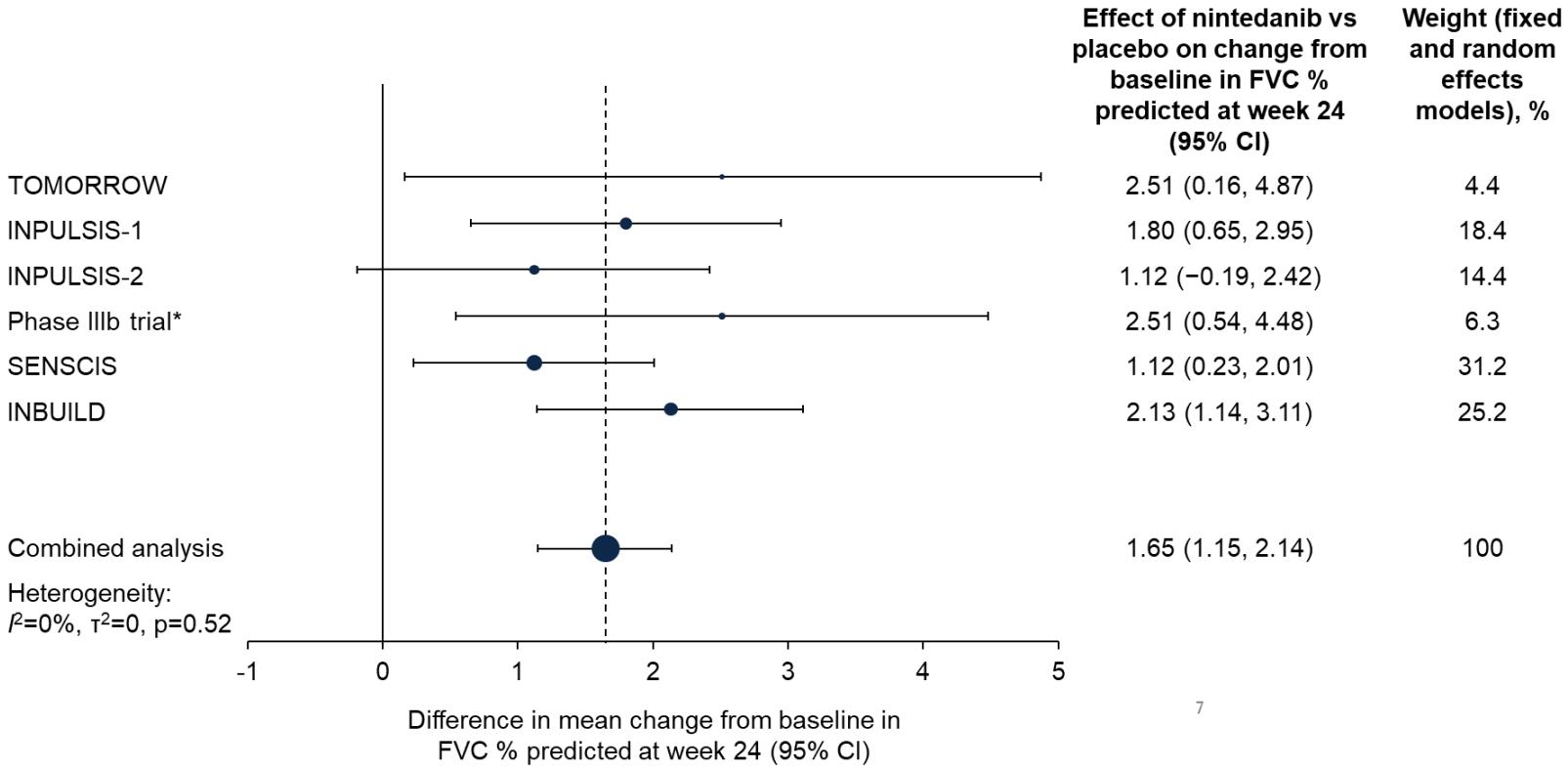
Figure S1. Change in height-for-age z-score over 24 weeks.



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.