Nintedanib in children and adolescents with fibrosing interstitial lung disease: the InPedILD trial

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INTRODUCTION

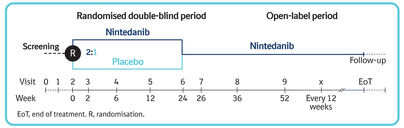
- Childhood ILD (chILD) is associated with significant morbidity and mortality.[1]
- It was postulated that nintedanib would provide benefit in patients with clinically significant fibrosing chILD based on:
  - Similarities in pathophysiology of fibrotic lung remodelling in adults and children[2]
  - The mode of action of nintedanib, which inhibits processes fundamental to the progression of lung fibrosis[3]
  - The established clinical benefit of nintedanib in adults with fibrosing ILDs of diverse aetiology:[4-6]

AIMS

- To evaluate data from the InPedILD trial on the dose-response and safety of nintedanib in children and adolescents with fibrosing ILD.
- To explore the effects of nintedanib on forced vital capacity (FVC) and oxygen saturation in this patient population.

METHODS

InPedILD trial design



EoT, end of treatment. R, randomisation.

Dosing of nintedanib

Weight range, kg*	Dose, bid	Reduced dose, bid†
13.5 to <23.0	50 mg	25 mg
23.0 to <33.5	75 mg	50 mg
33.5 to <57.5	100 mg	75 mg
≥57.5	150 mg	100 mg

*Patients with weight <13.5 kg were excluded from the trial. Dose was adjusted during treatment based on weight.
†Dose reductions (to the next dose) and treatment interruptions were permitted to manage adverse events.

Key inclusion criteria

- Age 6–17 years
- Evidence of fibrosing ILD on HRCT
- FVC ≥25% predicted
- Clinically significant disease
  - Fan score[7] ≥3:
    - » Symptomatic, normal resting room air saturation but abnormal saturation with sleep or exercise; symptomatic, abnormal resting room air saturation; symptomatic with pulmonary hypertension

  or
  - Evidence of clinical progression:
    - » Relative decline in FVC ≥10% predicted; relative decline in FVC of 5–10% predicted with worsening symptoms; worsening fibrosis on HRCT; other measures of clinical worsening attributed to progressive pulmonary fibrosis.

Co-primary endpoints

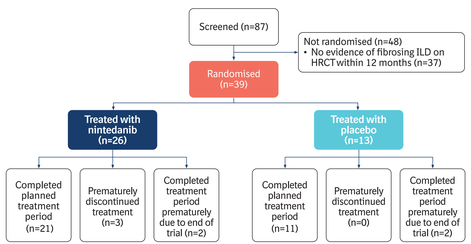
- Area under plasma concentration-time curve at steady state (AUC_{TSS}) at weeks 2 and 26 (i.e., week 2 of nintedanib treatment).
- Proportion of patients with treatment-emergent adverse events at week 24.

CONCLUSIONS

- Nintedanib had an acceptable safety and tolerability profile in children and adolescents with fibrosing ILD, with no new safety signals observed compared with adults.
- The exposure achieved with weight-based dosing was within the range observed in adults treated with 150 mg bid.
- Changes in FVC % predicted and SpO_2 over 24 weeks favoured nintedanib, but the trial was not powered for these exploratory endpoints.
- These data provide a scientific basis for the use of nintedanib in children and adolescents with fibrosing ILD (aged 6–17 years).

RESULTS

Patient disposition during double-blind period



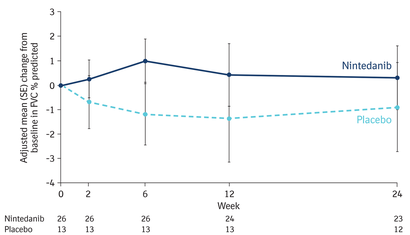
Pharmacokinetics of nintedanib

	InPedILD trial	
	Age 6 to 11 years (n=10)	Age 12 to 17 years (n=23)
AUC_{TSS} (ug·h/L) gMean (gCV%)	175 (85.1)	167 (83.6)

	Adults treated with nintedanib 150 mg bid[8]
AUC_{TSS} (ug·h/L) gMean (gCV%)	203 (67.5)
Median (5th, 95th percentile)	181 (81.5, 398)

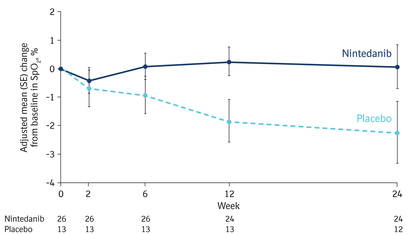
AUC_{TSS}, area under plasma concentration-time curve at steady state. gMean, geometric mean. gCV, geometric coefficient of variation.

Change in FVC % predicted over 24 weeks



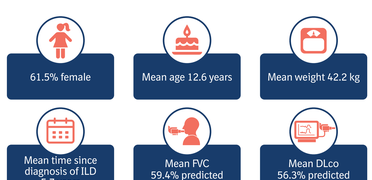
Adjusted mean (SE) change in FVC % predicted at week 24	Nintedanib: 0.3 (1.3) Placebo: −0.9 (1.8) Difference: 1.2 (95% CI: −3.4, 5.8)

Change in SpO_2 over 24 weeks



Adjusted mean (SE) change in SpO_2 at rest (%) at week 24	Nintedanib: 0.07 (0.77) Placebo: −2.25 (1.08) Difference: 2.31 (95% CI: −0.39, 5.02)

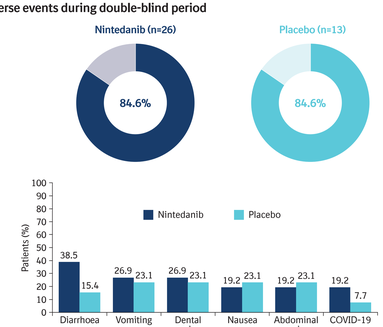
Baseline characteristics



Diagnoses

	n (%)
Surfactant protein deficiency	12 (30.8)
Systemic sclerosis	7 (17.9)
Toxic/radiation/drug-induced pneumonitis	4 (10.3)
Hypersensitivity pneumonitis	2 (5.1)
Other (diagnoses made in one patient)	14 (35.9)

Adverse events during double-blind period



% of patients with ≥1 such adverse event. Adverse events reported in >18% of patients in either treatment group based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Data are based on adverse events with onset from first intake of trial drug until day prior to first intake of open-label nintedanib or last intake of randomised treatment plus 28 days (whichever occurred first). Mean (SD) exposure to trial drug during double-blind period was 22.3 (4.8) weeks in the nintedanib group and 22.6 (4.2) weeks in the placebo group.

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