Study design of a Phase III, randomized, placebo-controlled trial of nintedanib in children and adolescents with clinically significant fibrosing interstitial lung disease (ILD)

Lisa R. Young,¹ Kevin K. Brown,² Matthias Griese,³ Gail Deutsch,⁴⁵ David Warburton,⁶⁷ Emily DeBoer,⁶⁷ Borian Voss,¹⁴ Ulrike Schmid,¹⁴ Rozsa Schlenker-Herceg,¹⁵ Daniela Verri,¹⁶ lorian Voss,¹⊸ Ulrike Schmid,¹⊸ Rozsa Schlenker-Herceg,¹⊸ Daniela Verri,¹⊸ Lorian Voss,¹⊸ Ulrike Schmid,¹⊸ Rozsa Schlenker-Herceg,¹⊸ Daniela Verri,¹⊸ Lorian Voss,¹⊸ Ulrike Schmid,¹⊸ Rozsa Schlenker-Herceg,¹⊸ Daniela Verri,¹⊸ Daniela Verri,¹⊸ Lorian Voss,¹⊸ Ulrike Schmid,¹⊸ Rozsa Schlenker-Herceg,¹⊸ Daniela Verri,¹⊸ Daniela Verri,¹⊸ Lorian Voss,¹⊸ Ulrike Schmid, Natural Verri, Natur Susanne Stowasser,¹⁷ Emmanuelle Clerisme-Beaty,¹⁷ Mihaela Dumistracel,¹⁷ Marilisa Schiwek,¹⁷ Kay Tetzlaff,¹⁷ Robin Deterding^{8,9}

¹Division of Pulmonary Medicine, The Children's Hospital of Philadelphia, Philadelphia ⁶Children's Hospital Los Angeles, Los Angeles, CA; ⁷Keck School of Medicine, University of Southern California, Los Angeles, CA; ⁸Section of Pediatric Pulmonary and Sleep Medicine, University of Southern California, Los Angeles, CA; ⁸Section of Pediatrics, University of Southern California, Los Angeles, CA; ⁸Section of Pediatrics, University of Southern California, Los Angeles, CA; ⁸Section of Pediatrics, University of Southern California, Los Angeles, CA; ⁸Section of Pediatrics, University of Southern California, Los Angeles, CA; ⁸Section of Pediatrics, University of Colorado, Aurora, CO; ⁹The Children's Hospital Colorado, Aurora, CO; ⁹The Child Edinburgh, United Kingdom; 11 Pediatric Pulmonary Department, Trousseau Hospital, AP-HP Sorbonne University, Paris, France; 12 Clinic for Pediatric Pulmonology, Allergology and Neonatology, Hannover, Germany; 13 Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI; 14 Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; 15 Boehringer Ingelheim Italia S.p.A, Milan, Italy; 17 Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

P574



CHILDHOOD INTERSTITIAL LUNG DISEASE (chILD)

>200 heterogeneous respiratory disorders

Conditions associated with fibrosing chILD include:

- Connective tissue disease-related ILD
- Radiation- and drug-inducedOther
- Surfactant dysfunction disorders



There are currently no approved treatments for fibrosing ILD in children



- Nintedanib, a tyrosine kinase inhibitor with a distinct inhibitory spectrum,1 has been shown to reduce the rate of decline in FVC
- In adult patients with IPF² and SSc-ILD³
- In patients with chronic fibrosing ILDs with a progressive phenotype, independent of fibrotic HRCT pattern⁴



A PHASE III CLINICAL TRIAL IN child (inPedilDTM)

OBJECTIVE: to evaluate the dose-exposure relationship and safety of nintedanib in children with fibrosing ILD

- Multicenter, double-blind, randomized trial 1199-0337
- ClinicalTrials.gov: NCT04093024

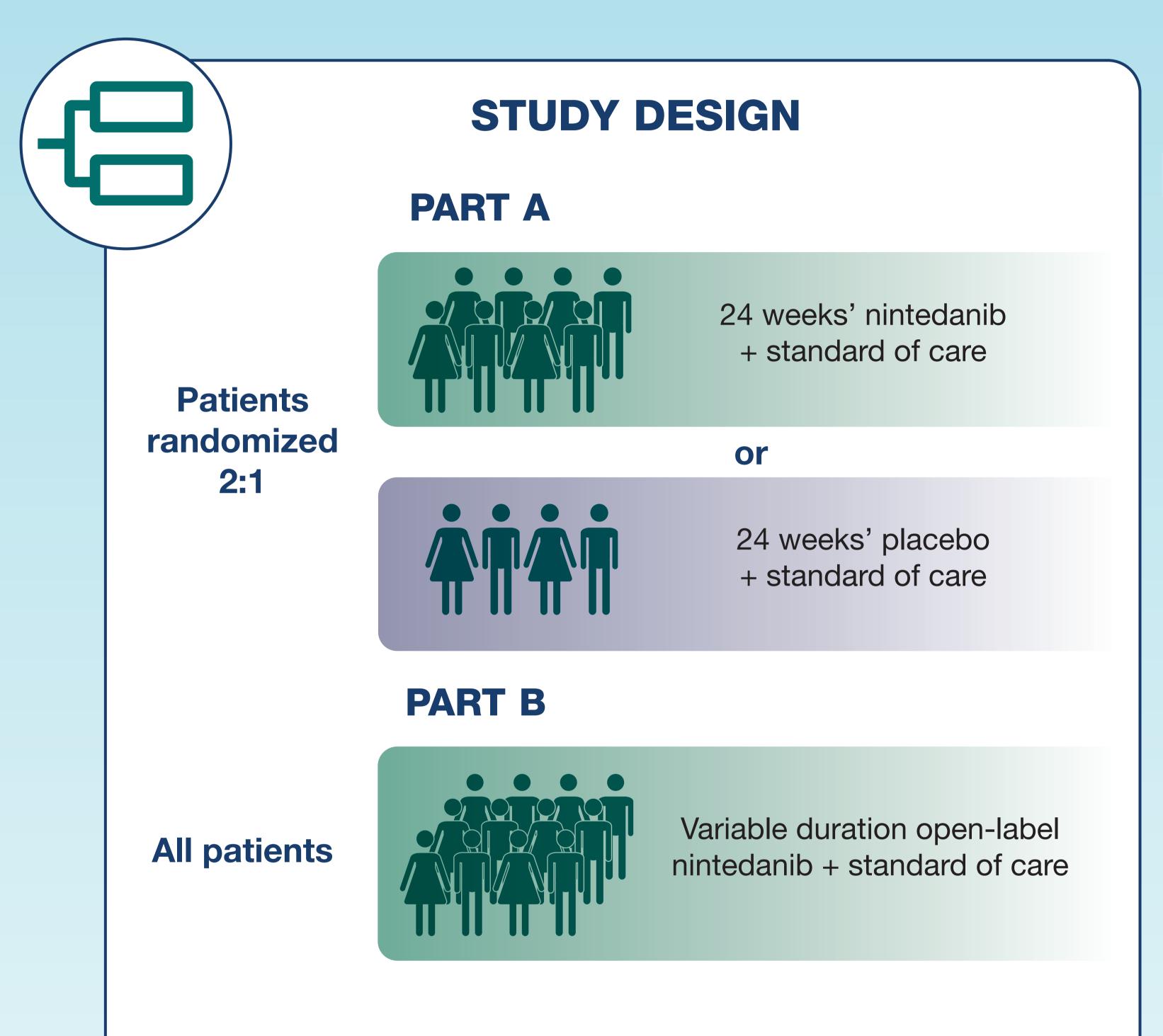
TARGET RECRUITMENT



≥30 patients



End of recruitment will be when ≥30 patients (≥20 adolescents aged 12–17 years) have completed PK sampling at 26 weeks or have prematurely discontinued the trial



DOSING



Twice-daily dosing



Doses are based on patient weight using allometric scaling to match

the adult dose



Single-step dose reduction or interruption are allowed to manage adverse events

KEY INCLUSION CRITERIA

- Aged 6–17 years
- Evidence of fibrosing ILD
- FVC ≥25% predicted
- Clinically significant disease:
- Fan score ≥3, or
- Evidence of clinical progression over time:
- » 5–10% relative decline in FVC % predicted + worsening symptoms
- » ≥10% relative decline in FVC % predicted
- » Increased fibrosis on HRCT
- » Other measures, e.g. increased oxygen requirement, decreased diffusion capacity



Evidence of fibrosing ILD, as confirmed by central review

Lung biopsy – previous findings of fibrosis:

- NSIP (fibrosing)
 UIP
 honeycomb lung
- evidence of interstitial fibrosis on a significant component
- evidence of lobular remodeling on a significant component



- ≥1 of the following on 1 **HRCT** scan within
- 12 months of screening:^a reticular abnormality
- traction bronchiectasis
- architectural distortion^b
- honeycombing

KEY EXCLUSION CRITERIA

Underlying chronic liver

Cardiovascular disease

(defined by protocol)

disease

Significant PAH

Bleeding risk

- ≥2 of the following on ≥2 HRCT scans; most recent within 12 months of screening:
- reticular abnormality
- traction bronchiectasis
- architectural distortion^b
- honeycombing cystic abnormalities



Meets criteria for fibrosing ILD

^aCo-existing cystic abnormalities or ground-glass opacity are acceptable; however, co-existing multifocal, non-fibrotic, non-dependent consolidations (e.g. organizing pneumonia, infection) will not be permitted. ^bWith or without ground-glass opacification.



PRIMARY ENDPOINTS

- Pharmacokinetics AUC_{TSS} (Weeks 2 & 26)
- Treatment-emergent adverse events (Week 24)

SECONDARY ENDPOINTS

- Pathologic findings of epiphyseal growth plate (Weeks 24 & 52)
- Pathologic findings on dental examination or imaging (Weeks 24) & 52)
- Treatment-emergent adverse events (whole trial)
- Change in height, sitting height and leg length from baseline (Weeks 24, 52, 76 & 100)
- FVC % predicted change from baseline (Weeks 24 & 52)
- Oxygen saturation in air change from baseline (Weeks 24 & 52)
- Pediatric Quality of Life Questionnaire (PedsQLTM) (Weeks 24 & 52)
- 6-minute walk distance change from baseline (Weeks 24 & 52)
- Additional efficacy and safety endpoints (over longer term)



CONCLUSIONS

- This Phase III trial will characterize the dose-exposure relationship and safety of nintedanib in children and adolescents with fibrosing ILD
- The design of this study has prompted new thinking around the definitions and outcome measures of pulmonary fibrosis in children

#PedILD



References

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Conflicts of interest

LRY reports personal fees from Boehringer Ingelheim, grants from NIH and royalties for authorship from UpToDate. RD reports nonfinancial support and personal fees from Boehringer Ingelheim, and that she is founder and president of Now Vitals, Inc., founder and consultant and has received personal fees from Triple Endoscopy, Inc. and is founder and chief medical officer at Erables, Inc.

Disclosures

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Abbreviations

AUC_{rss}, area under the plasma concentration-time curve at steady state; chILD, childhood interstitial lung disease; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; PAH, pulmonary arterial hypertension; PK, pharmacokinetics; SSc-ILD, systemic sclerosis-associated interstitial lung disease; UIP, usual interstitial pneumonia.

