NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	(b) (4) Supplement
Application Number(s)	NDA 205832-023
Priority or Standard	Priority
Submit Date(s)	5/19/23
Received Date(s)	5/19/23
PDUFA Goal Date	11/17/23
Division/Office	Division of Pulmonology, Allergy, and Critical Care/Office of Immunology and Inflammation
Review Completion Date	
Established/Proper Name	Nintedanib
(Proposed) Trade Name	Ofev
Pharmacologic Class	Tyrosine Kinase Inhibitor
Code name	
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Dosage form	Capsules
Applicant proposed Dosing Regimen	
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	(b) (4)
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	Not applicable

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
OMPI = Office of Medical Policy Initiatives
DMEPA=Division of Medication Error Prevention and Analysis
DMPP = Division of Medical Policy Programs
PLT= Patient Labeling Team

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant, Boehringer Ingelheim (BI), has submitted a supplemental New Drug Application (sNDA) (b) (4) Nintedanib (tradename OFEV) is a small molecule receptor and non-receptor tyrosine kinase inhibitor (including but not limited to platelet-derived growth factor receptor, fibroblast growth factor receptor, vascular endothelial growth factor receptor, and Fms-like tyrosine kinases). It is approved for the treatment of idiopathic pulmonary fibrosis (IPF), systemic sclerosis interstitial lung disease (SSc-ILD), and chronic fibrosing ILD with a progressive phenotype, at a dosage regimen of 150 mg oral twice daily.

When nintedanib was approved for chronic fibrosing ILDs with a progressive phenotype on 3/9/2020, a PREA post-marketing requirement (PMR) study issued. This PMR (3807-1) was as follows:

> Conduct a randomized double-blind placebo-controlled trial of ≥24 weeks in pediatric patients ages 6 to less than 18 years with fibrosing interstitial lung disease with a progressive phenotype. The objective of this trial will be to characterize the pharmacokinetics and safety in this population, as well as collect efficacy data.

A Written Request (WR) was also issued on 10/27/2020. To support this sNDA and to address PMR 3807-1 and the WR, the Applicant has submitted data from pediatric study 1199.337.

1.2. Conclusions on the Substantial Evidence of Effectiveness

(b) (4)

The Applicant completed Study 1199.337 (Study 337), a randomized, placebo-controlled, 2-part (part A: fixed 24-week treatment period, part B: variable duration) safety/PK study in patients ages 6 to 17 years old with ILD. The patients enrolled had ILDs due to various etiologies (e.g., surfactant protein deficiency, systemic sclerosis) and were all either severe and/or progressive (based on worsening imaging, radiography, and/or symptoms). The primary endpoint was safety/PK, and secondary endpoints included various efficacy measures (e.g., FVC, 6MW, SpO2). Given feasibility issues with patient enrollment due to the rarity of the disease, this trial was not designed with efficacy as the primary objective. However, to aid in the interpretation of the

efficacy, in addition to frequentist statistical analyses, Bayesian efficacy analyses were performed using pre-specified methods which borrowed adult data from nintedanib trials in adults ILDs.

With regard to efficacy, results from both the FVC and non-FVC related endpoints did not provide support for efficacy based on frequentist analyses. Point estimates for results from traditional (frequentist) statistical analyses for change-in-FVC endpoints were modest (1.2% treatment difference) and 95% confidence intervals included the null value. Results from pre-specified Bayesian analyses were such that a high degree of borrowing from adult data was needed (90%) in order to achieve results where the 80% credible interval excluded the null for the pre-specified Bayesian weight (0.56). Moreover, in order to achieve 95% credible intervals that excluded the null (which is more typically used in Bayesian analyses) borrowing of 94% from adult data was necessary. Such a high degree of borrowing would equate to near full extrapolation of pediatric treatment effect from adult data. Close to full extrapolation does not appear to be scientifically justified given the notable differences in the adult and pediatric conditions (see section 2.1), and the differences observed in the underlying causes of ILD in pediatric patients enrolled in Study 337 compared to the underlying causes observed from the adult ILD trials from which data were borrowed. Overall, based on these data, there remains considerable uncertainty regarding the benefit of nintedanib in this pediatric population; the data are insufficient to support the efficacy of nintedanib for the treatment of fibrosing interstitial lung diseases (ILD) in patients 6 to 17 years of age.

(b) (4) trial results also raised safety concerns related to weight loss and dental adverse effects, both of which were plausible based on either adult data (USPI label section 6, weight loss) or nonclinical studies (dentopathy in mouse studies). These safety concerns are noteworthy as they were observed in a small trial of relatively short duration and are relevant to the pediatric population given their expected growth and development.

(b) (4) the benefit-risk assessment is not favorable for nintedanib for the treatment of fibrosing interstitial ILD in patients 6 to 17 years of age.

In conclusion, (b) (4) Study 337 has fulfilled PREA PMR 3807-1 and has addressed the WR issued on 10/27/2020. In order to provide clinicians with the pediatric data generated from Study 337, (b) (4) the Division will also request that the Applicant submit a labeling supplement to amend Section 8.4 of the USPI to include results from Study 337.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pediatric ILD is a rare pediatric condition which describes a grouping of various ILDs in patients < 18 years of age from a variety of causes, such as drugs/radiation/toxin exposures, hypersensitivity pneumonitis, congenital/familial conditions (e.g., surfactant protein deficiency), or autoimmune conditions (e.g., sJIA). Although most patients have stable or resolving disease, there is a subset that have progressive disease. While there are some similarities between pediatric ILD and adult ILDs (e.g., common etiologies [such as hypersensitivity pneumonitis], many of the clinical features of pediatric ILD do not overlap with adult ILDs.

The Applicant conducted a single study, Study 337, which was a 2-part, randomized, double-blinded, placebo-controlled trial in pediatric patients ages 6 to 17 years to evaluate the safety, PK, and exploratory efficacy of nintedanib in pediatric ILD. Efficacy endpoints included lung function (FVC) as well as non-FVC related endpoints. Due to the rarity of the disease, this trial was not designed with efficacy as the primary objective. However, to aid in the interpretation of the efficacy, in addition to frequentist statistical analyses, Bayesian efficacy analyses were performed using pre-specified methods.

In Study 337, both the FVC and non-FVC related endpoints, did not provide support for efficacy. Point estimates for results from traditional (frequentist) statistical analyses for change-in-FVC endpoints were numerically modest and 95% confidence intervals included the null value. Moreover, results from Bayesian analyses were such that a large degree of borrowing of adult data (>90%) would have been necessary to allow for credible intervals that excluded the null. Such a high degree of borrowing from adult ILD data is not scientifically justified given the known differences between pediatric ILD and adult ILD. Notwithstanding these issues, point estimates for the FVC analyses were modest regardless of the statistical methodology used (frequentist or Bayesian). Furthermore, trial results also raised safety concerns related to weight loss and dental adverse effects, both of which were plausible based on either adult data (USPI label Section 6, weight loss) or nonclinical studies (dentopathy in mouse studies). These safety concerns are noteworthy, as they were observed in a small trial of relatively short duration and are relevant to the pediatric population given their expected growth and development.
Given that these data are insufficient to support efficacy and considering that safety concerns were identified, the benefit-risk balance is not favorable for nintedanib for the treatment of fibrosing interstitial ILD in patients 6 to 17 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric ILD is a rare pediatric condition which describes a grouping of various ILDs in patients < 18 years of age from a variety of causes, such as drugs/radiation/toxin exposures, hypersensitivity pneumonitis, congenital/familial conditions (e.g., surfactant protein deficiency), or autoimmune conditions (e.g., sJIA). • While there are some features of pediatric ILD that overlap with adult ILDs, there are many differences (e.g., likely clinical trajectory, radiography, histopathology). • It is unclear why some patients in adult or pediatric ILDs have progressive disease, while other patients do not.	There are many differences between pediatric ILDs (a grouping of various ILDs in patients < 18 years of age) and adult ILDs. However, based on the possibility of a potential pathobiologic overlap between adults and pediatric patients with progressive disease, it may be reasonable to study adult therapeutic options in pediatric ILD.
Current Treatment Options	• There are no approved treatments for any pediatric ILD • Management of patients with pediatric ILD includes supportive care and trial of various drugs based on expert opinion. • Drug therapies that may be considered in the management of pediatric ILD include immunomodulators or immunosuppressants (e.g., mycophenolate mofetil, prednisone, hydroxychloroquine).	Because there are no approved therapies for pediatric ILD, there is unmet need. Treatment of patients with pediatric ILD is based on supportive care and trial of immunomodulatory medications.
Benefit	• Results from FVC analyses comparing nintedanib to placebo treated patients show a modest point estimate with 95% confidence intervals that include the null. • Other efficacy endpoints (SpO2, 6MW, PedsQoL) did not provide support for a treatment effect. • Results from Bayesian FVC analyses do not provide clear support for a treatment effect for nintedanib in pediatric ILD. A large degree of adult patient data borrowing (>90%) would be needed in order for credible intervals (as low as 80%) to exclude the null value.	There is no meaningful support for a benefit of nintedanib in pediatric patients. Bayesian analyses were pre-specified to aid in the interpretation of the efficacy, due to the rarity of the condition. However, a large degree of borrowing of adult data was needed to exclude the null value for the pre-specified 80% credible interval. Such a degree of borrowing does not appear to be warranted given the current understanding of the differences between pediatric ILD and adult ILDs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The small sample size and 24-week study duration limit the ability to make definite safety conclusions. • There are safety concerns raised for weight loss and dental adverse events, particularly in the growing pediatric population that was studied in Study 337 • Safety concerns were also noteworthy as they were identified in a small, relatively short trial.	Safety concerns related to weight loss and dental adverse events were identified and are notable in the context of the pediatric population with expected active growth and development. (b) (4)

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		X☐	Patient reported outcome (PRO)	Section 8.1.2
		X☐	Observer reported outcome (ObsRO)	Section 8.1.2
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Pediatric interstitial lung disease (ILD) is sometimes referred to as childhood interstitial lung disease (chILD). Given that patients with this condition may not have exclusive interstitial involvement, there is a lack of consensus on use of the term chILD and some have suggested using the term diffuse lung disease (DLD). In this review, the term pediatric ILD is used to facilitate comparison with adult ILDs.

Pediatric ILD is a grouping of heterogeneous conditions, with an estimated prevalence ranging from 1.5 to 3.6 cases/million[1,2], making it a rare pediatric disease. While the clinical course for the majority of children and adolescents with ILD is that of resolution or stability, progressive disease has been described[3]. Why certain pediatric patients progress while others do not is not understood, and this is confounded further by etiologic variability. There are many potential causes of pediatric ILDs that can vary widely, and include surfactant protein deficiencies, familial/congenital conditions, autoimmune conditions, and toxic/drug/radiation exposures. In the vast majority of pediatric ILD cases, histopathologic changes include inflammation with pneumocyte damage and compensatory hyperplasia, without architectural distortion of the underlying lung. However, the histopathology can vary significantly and may include findings of granular or proteinaceous material deposition in the distal airspaces (e.g., PAP) or foamy alveolar macrophages (e.g., desquamative interstitial pneumonitis [DIP]), particularly in abnormal surfactant related conditions. The radiographic features generally reflect the histopathology, and thus include ground glass changes consistent with desquamative interstitial pneumonia (DIP) or non-specific interstitial pneumonitis (NSIP).

With regard to adult ILDs, the most common adult progressive ILD is idiopathic pulmonary fibrosis (IPF). IPF is a serious fatal disease, with a 2–5-year median survival, and one that involves significant architectural distortion of the lung – reflected in histopathology and radiography showing usual interstitial pneumonitis (UIP). In addition to IPF, there are subsets of patients with other diagnosed ILDs (e.g., hypersensitivity pneumonitis, sarcoidosis) that may have rapidly progressive fibrotic disease, collectively referred to using a recently adopted term as progressive pulmonary fibrosis (PPF) [4]. Although an underlying etiology may be present for patients with PPF (e.g., rheumatoid arthritis), it is not known why some adult patients with a

[1] Dinwiddie R et al. Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. Pediatr Pulmonol 2002;34(1):23–29.
[2] Saddi V et al. Childhood interstitial lung diseases in immunocompetent children in Australia and New Zealand: a decade's experience. Orphanet J Rare Dis 2017;12:133.
[3] Clement A et al. Interstitial lung diseases in children. Orphanet J Rare Dis 2010 Aug 20:5:22. doi: 10.1186/1750-1172-5-22
[4] Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. https://doi.org/10.1164/rccm.202202-0399ST

given ILD progress rapidly while others do not. Nevertheless, these patients also have a clinical trajectory similar to IPF, and many PPF patients have radiography and histopathology similar to IPF as well (i.e., UIP).

Comparing (and contrasting) pediatric ILD to adult progressive ILDs can help determine whether a meaningful overlap may be present between the two conditions. While certain etiologies may be common between PPF and pediatric ILD (e.g., hypersensitivity pneumonitis or systemic sclerosis ILD), there are etiologies that are specific to either pediatric ILD or adult ILDs (e.g., surfactant disorders and IPF are only noted in pediatric and adult patients, respectively). The majority of clinical characteristics are different between the adult and pediatric conditions. For example, radiography and histopathology differ considerably between pediatric ILD and PPF: UIP is rarely observed in pediatric ILD[5], whereas UIP is the most common HRCT pattern seen in IPF and PPF. Similarly, prognosis differs considerably: median survival in IPF and PPF is poor (~2-5 years), whereas the majority of pediatric ILD cases (~85%) carry a favorable prognosis. As such, the clinical overlap between adult progressive ILDs (i.e., IPF/PPF) and pediatric ILDs is limited at best, and the degree to which data regarding adult ILDs can be applied to pediatric ILDs is uncertain.

However, in the absence of approved therapies (see Section 2.2), it may be reasonable to consider studying adult ILD treatments for the treatment of pediatric ILDs, particularly for severe and progressive pediatric ILD patients. In addition, because the pathogenesis of pulmonary fibrosis (in adults or pediatric patients) has not been fully elucidated, particularly rapid progression, it is conceptually possible that a shared pathobiology between progressive adult ILDs and progressive pediatric ILDs may be present. It is in this context that the Applicant has studied nintedanib, approved for use in various adult ILDs, in pediatric ILDs.

2.2. Analysis of Current Treatment Options

There is currently no approved treatment for any pediatric ILD.

General management is largely driven by expert opinion and is supportive in nature (including limiting exposure to triggering agent, encouraging supervised exercise, providing oxygen when needed, nutritional support, bronchodilators for reversible airway obstruction, and vaccination maintenance). Such supportive measures are combined with trials of various immunomodulators, depending on disease severity and progression. For example, hydroxychloroquine (with or without corticosteroids) is used for surfactant dysfunction-related pediatric ILDs; cyclophosphamide or mycophenolate mofetil is used for juvenile SSc-related ILD; corticosteroids may be used for hypersensitivity pneumonitis, lymphocytic interstitial pneumonia, cryptogenic organizing pneumonia, eosinophilic pneumonia, or sarcoidosis.

[5] Nathan N et al. Pulmonary Fibrosis in Children. J. Clin. Med. 2019, 8, 1312; doi:10.3390/jcm8091312

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nintedanib has been marketed in the US since 2014 for the treatment of IPF (NDA 205832). It was also approved to slow the rate of decline in pulmonary function in patients with SSc-ILD (September 2019), and for the treatment of adults with chronic fibrosing interstitial lung diseases with a progressive phenotype (March 2020).

3.2. Summary of Presubmission/Submission Regulatory Activity

A summary of the regulatory activity relevant to this supplemental NDA is as follows:

1) Supplemental NDA 205832-013 (nintedanib for chronic fibrosing ILD with a progressive phenotype) was approved on 3/9/2020. At the time of approval of supplement 013, PREA PMR 3807-1 was issued as follows:

   Conduct a randomized double-blind placebo-controlled trial of ≥24 weeks in pediatric patients ages 6 to less than 18 years with fibrosing interstitial lung disease with a progressive phenotype. The objective of this trial will be to characterize the pharmacokinetics and safety in this population, as well as collect efficacy data.

   Studies in patients <6 years of age were waived as there is evidence strongly suggesting that the drug product would be ineffective and/or unsafe in this pediatric group, such that the risk-benefit profile in this age group would not favor nintedanib use.

2) On 7/14/2020, a proposed pediatric study request (PPSR) was submitted (b) (4) In response, a Written Request (WR) was issued on 10/27/2020. In general, the parameters for the WR study design, population, assessments, and objectives, were aligned with the PREA PMR 3807-1.

3) A WR amendment (amendment 1) was issued by the Division on 4/12/2021 with several key revisions to the original WR made:
   (b) (4)

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were performed. However, the following bioanalytical site was selected from the study 1199-0337 for inspection by CDER Office of Clinical Pharmacology (OCP).

- (b) (4)

Office of Study Integrity and Surveillance (OSIS) conducted a Remote Record Review (RRR) for (b) (4) which falls within the surveillance interval. The RRR was conducted under the following submissions: NDA (b) (4) OSIS concluded that data from the reviewed studies were reliable.

Therefore, OSIS concluded based on the rationale described above, inspections are not warranted at this time.

4.2. Product Quality

CMC information (b) (4) is also provided in Module 3.

(b) (4)

There were no issues noted in the review of Drs. Chong Ho Kim and Ramesh Raghavachari.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This supplement contained no nonclinical data. All nonclinical data (b) (4) had been previously submitted and reviewed in the original NDA. The current nonclinical review focuses on the evaluation of the effects of nintedanib on growth and development in young animals. The review found that nintedanib affected bone and tooth development in young animals (i.e., mice, rats, and monkeys). These findings may be relevant to the safety assessment of nintedanib in pediatric use because tyrosine kinase inhibitors such as nintedanib play a significant role in bone remodeling.

5.2 Toxicology

Toxicity Studies in Young Animals

Nintedanib affects bone and tooth development in young animals. Effects of nintedanib on bone and tooth development were studied in mice, rats, and monkeys (Studies U10-1798, U05-1843, and U10-1875). These studies were reviewed previously in the original NDA review and related IND reviews (DARRTS ID# 3618575, 2841259, and 2944664). (b) (4) Dr. Luqi Pei completed a comprehensive re-evaluation of bone and tooth development findings observed in these studies in a nonclinical review completed on September 15, 2023 (DARRTS ID# 5244859). Below is a summary of the findings of the re-evaluation. See Section 19.3 and Dr. Pei's review for details.

Young animals (mice, rats, and monkeys) were dosed orally with up to 100-mg/kg/day nintedanib for up to 52 weeks. The age of the animals when dosing started was approximately 5.5, 8.5, and 133 weeks in mice, rats, and monkeys, respectively. The treatment duration was up to 13, 26, and 52 weeks in mice, rats, and monkeys, respectively. The nintedanib dose was up to 100, 80, and 60 mg/kg/day in mice, rats, and monkeys, respectively.

Treatment-related effects were observed in the bone and teeth. The bone effect (e.g., thickening of growth plate of long bones) was observed in every species studied. Dentopathy was observed in rodent species only. The findings in rats and monkeys were not readily reversible. The reversibility in mice was unknown.

6 Clinical Pharmacology

6.1. Executive Summary

On 05/19/2023, the Applicant, Boehringer Ingelheim Pharmaceuticals, Inc., submitted (b) (4) supplement under NDA 205832 (supplement 23) (b) (4)

(b) (4)

Ofev has been approved for

- Treatment of idiopathic pulmonary fibrosis (IPF) in adults
- Treatment of chronic fibrosing ILDs with a progressive phenotype in adults
- Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)

The recommended dosage in adult patients is 150 mg orally twice daily (BID) approximately 12 hours apart taken with food.

In this submission, the Applicant characterized the pharmacokinetics (PK) of nintedanib in pediatric patients 6 to 17 years old in Study 1199-0337 which was a double blind, randomized, placebo-controlled trial (N=39). The systemic exposures in pediatric patients 6 to 17 years old with ILDs following (b) (4) dosing regimens are comparable to adult patients with ILDs following the approved 150 mg BID dosing regimen. However, the exposure response

relationship cannot be adequately characterized with the limited sample size of pediatric patients. Given the heterogeneity of the clinical features between adult patients with ILD and pediatric patients with ILDs, efficacy response cannot be extrapolated to pediatric patients with the matched systemic exposure.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology and the Division of Pharmacometrics have reviewed this submission under NDA 205832/S-023. The Clinical Pharmacology review team defers to Clinical and Statistical reviewers for the assessment of efficacy and safety.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Nintedanib is a small molecule tyrosine kinase inhibitor for platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3. In addition, nintedanib inhibits Flt-3, Lck, Lyn and Src kinases.

Nintedanib reached maximum plasma concentrations approximately 2 to 4 hours after oral administration as a soft gelatin capsule under fed conditions. The absolute bioavailability of a 100 mg dose was 4.7% (90% CI: 3.62 to 6.08) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.

After food intake, nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (90% CI: 95.3% to 152.5%) and absorption was delayed (median Tmax fasted: 2.00 hours; fed: 3.98 hours), irrespective of the food type.

The effective half-life of nintedanib in patients with IPF was 9.5 hours (gCV 31.9%). Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min; gCV 28.8%). Urinary excretion of unchanged drug within 48 hours was about 0.05% of the dose after oral and about 1.4% of the dose after intravenous administration; the renal clearance was 20 mL/min.

The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

(b) (4) were investigated in the pediatric Study 1199-0337.

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

What are the pharmacokinetic characteristics of nintedanib in children and adolescents with clinically significant fibrosing interstitial lung disease?

The Applicant conducted a double blind, randomized, placebo-controlled study (Study 1199-0337) to evaluate the PK and safety of nintedanib in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD. The studied dosing regimen and dose reduction possibilities are listed in Table 2 below. If a patient experienced a drug-related adverse event (AE), the dose could be reduced to the next lower dose and the dose could be re-started after recovery. If the reduced dose was well tolerated, re-escalation was possible within 4 weeks after dose reduction in case of AEs considered drug-related, or within 8 weeks in case of AEs not considered drug-related.

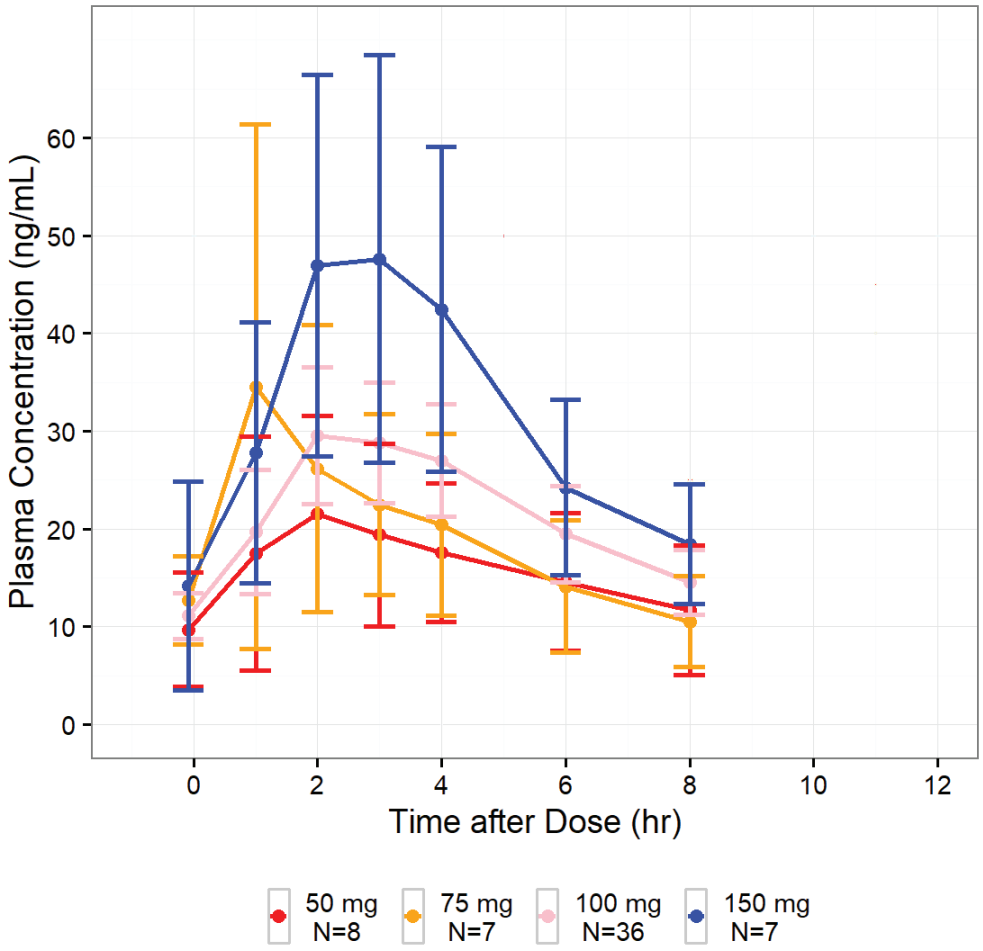
Table 2: Dose assignment and dose reduction possibilities based on body weight bins according to ICH E11

Bodyweight Bin	Weight Range	Assigned Dose	Capsule Strength	Dose Reduction	Reduced Capsule Strength
1	13.5 to <23.0 kg	50 mg BID	25 mg	25 mg	25 mg
2	23.0 to <33.5 kg	75 mg BID	25 mg	50 mg	25 mg
3	33.5 to <57.5kg	100 mg BID	100 mg or 25 mg	75 mg	25 mg
4	≥57.5 kg	150 mg BID	150 mg or 25 mg	100 mg	100 mg or 25 mg

Source: Table 9: 1 in Clinical Study Report 1199-0337

In Study 1199-0337, rich sampling PK samples were collected for each subject on Day 15 and Day 183 post-dose. The mean plasma concentration time profiles of nintedanib are depicted in Figure 1 and Figure 2, and the descriptive statistics of PK parameters are listed in Table 3 and Table 4.

Figure 1: Nintedanib Plasma Concentration Time Profiles (mean with 95% confidence interval) by dose



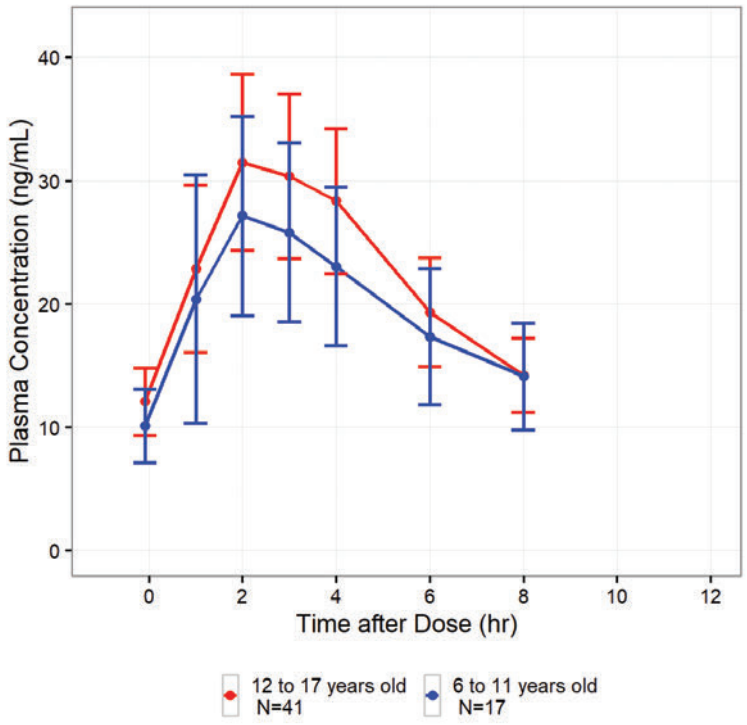
Source: reviewer's analysis based on adpc.xpt
N represents the total number of PK profiles at Day 15 and Day 183

Table 3: Comparison of Geometric Mean and median PK parameters (pooled for Day 15 and Day 183) after multiple oral administration of nintedanib by dose group (based on noncompartmental analysis)

Dose	Parameter	Unit	N	GeoMean	GeoCV	Median	Min	Max
50	AUCTAU	h*ng/mL	7	136.2	89.2	141.4	50.9	354.7
50	CMAX	ng/mL	7	21.5	80.8	22.3	8.7	53.2
75	AUCTAU	h*ng/mL	7	149.8	88.9	178.2	42.2	329.1
75	CMAX	ng/mL	7	31.3	110.0	31.6	6.4	104.0
100	AUCTAU	h*ng/mL	33	164.4	69.7	157.2	48.5	553.0
100	CMAX	ng/mL	33	32.6	72.2	33.8	6.5	89.2
150	AUCTAU	h*ng/mL	7	271.2	47.1	254.1	130.8	515.0
150	CMAX	ng/mL	7	55.1	42.0	55.9	34.4	99.5

Source: reviewer's analysis based on adpp.xpt

Figure 2: Comparison of Nintedanib Plasma Concentration Time Profiles (mean with 95% confidence interval) in Children (6 to 11 years old) and Adolescents (12 to 17 years old)



Source: reviewer's analysis based on adpc.xpt
N represents the total number of PK profiles at Day 15 and Day 183

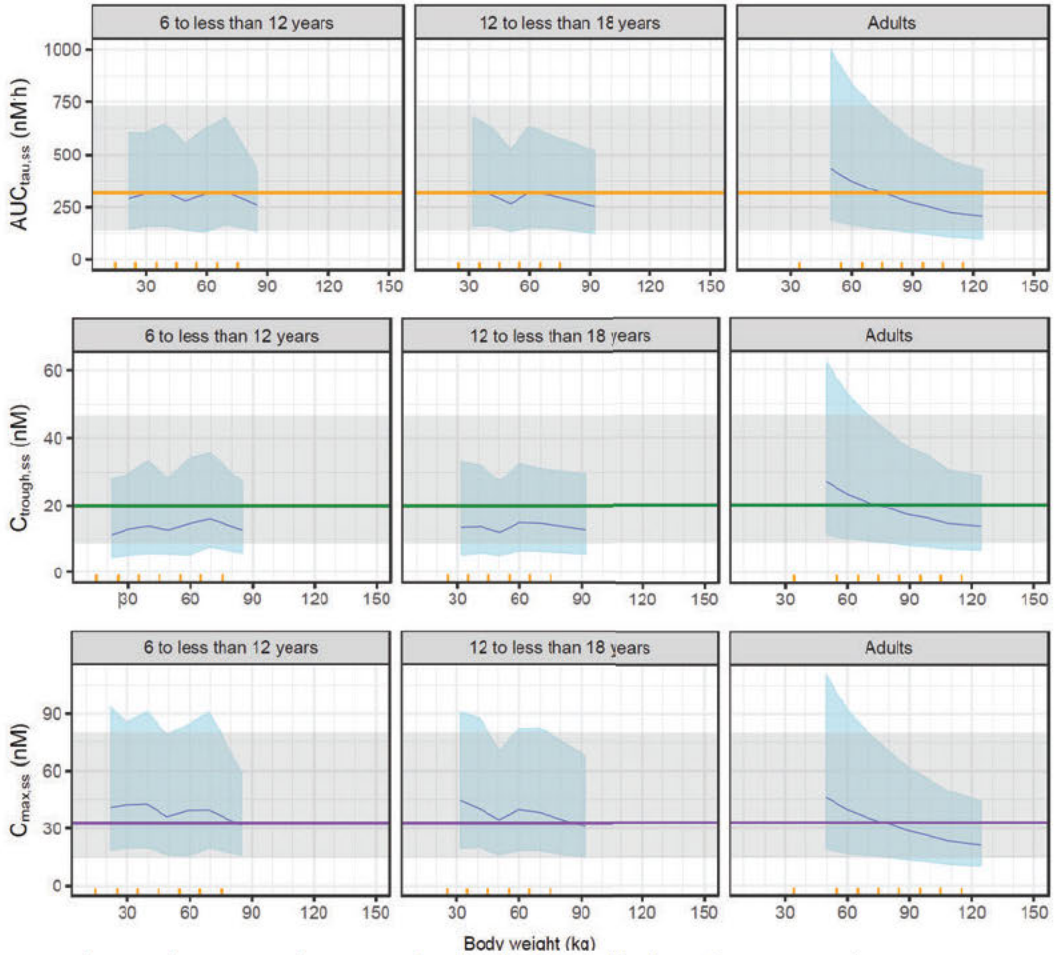
Table 4: Comparison of Geometric Mean and median PK parameters (pooled for Day 15 and Day 183) after multiple oral administration of nintedanib by age group over all treatments (based on noncompartmental analysis)

PK parameter	6 - <12 years			12 - <18 years		
	N	gMean (gCV)	Median (min, max)	N	gMean (gCV)	Median (min, max)
$AUC_{\tau,ss}$ [ng·h/mL]	10	175 (85.1)	220 (50.9, 472)	23	167 (83.6)	188 (42.2, 515)
$C_{max,ss}$ [ng/mL]	10	28.7 (85.1)	33.9 (8.68, 82.7)	25	33.0 (90.7)	35.1 (6.39, 99.5)
$t_{max,ss}$[1] [h]	10	-	2.00 (0.917, 4.17)	25	-	2.67 (0.917, 5.75)
$t_{1/2,ss}$ [h]	10	5.37 (80.9)	4.56 (2.74, 29.3)	23	3.82 (42.7)	3.31 (2.28, 11.3)
CL/F_{ss} [mL/min]	10	6800 (60.1)	6820 (2840, 16 400)	23	10 300 (79.5)	10 100 (3800, 34 300)
V_z/F_{ss} [L]	10	3160 (88.7)	2700 (1620, 18 500)	23	3420 (115)	2880 (1100, 26 600)

1 For $t_{max,ss}$, only median and range (minimum, maximum) are displayed.
Source: Table 11:29 in Clinical Study Report 1199-0337

The Applicant also conducted a population PK (PopPK) analysis with pediatric PK data. Based on the PopPK model, the Applicant simulated exposure metrics (AUCss, Cmax,ss, and Ctrough,ss) following the proposed dosing regimen in children and adolescents and the approved dosing regimen in adults. See Pharmacometrics review in Section 19.4 for details. The simulated PK metrics in children, adolescents, and adults are depicted in Figure 3.

Figure 3: Predicted nintedanib Cmax,ss, Ctrough,ss Cav,ss and AUCτ,ss versus WT and age, for the PK simulation data set



Source: Figure 36 in Pop PK and pop PKPD for nintedanib in pediatric ILD (c37084509-03)
The blue line is the geometric mean and the blue area spans the 5th to 95th percentiles, for each WT bin. As reference, the gray area spans the 5th to 95th percentiles across all adults and the horizontal line indicates the geometric mean (Cmax,ss (purple), Ctrough,ss (green), Cav,ss (red) and AUCτ,ss (orange): 33 nM, 20 nM, 26 nM and 316 nM.h, respectively) of the adult population. An orange rug (brush border) along the x-axis indicates the lowest WT in each WT bin.

The [redacted] (b) (4) dosing regimen in children and adolescents showed similar exposure (e.g., AUCss, Ctrough,ss, and Cmax,ss) when compared to adults subjects.

Is [redacted] (b) (4) dosing regimen appropriate for the general patient population [redacted] (b) (4) ?

The Applicant conducted an exposure response (ER) analysis for FVCpp (percent predicted forced vital capacity) and FVC z-score [redacted] (b) (4) using a Bayesian approach. The ER analysis adopted ER relationship established in adult patients with ILDs as prior. Given the limited sample size of pediatric patients enrolled in Study 1199-0337 (N=13 for

placebo and N=26 for nintedanib), the post hoc estimates of the ER relationship in children are mainly driven by the adult prior. See pharmacometrics review in Section 19.4 for details.

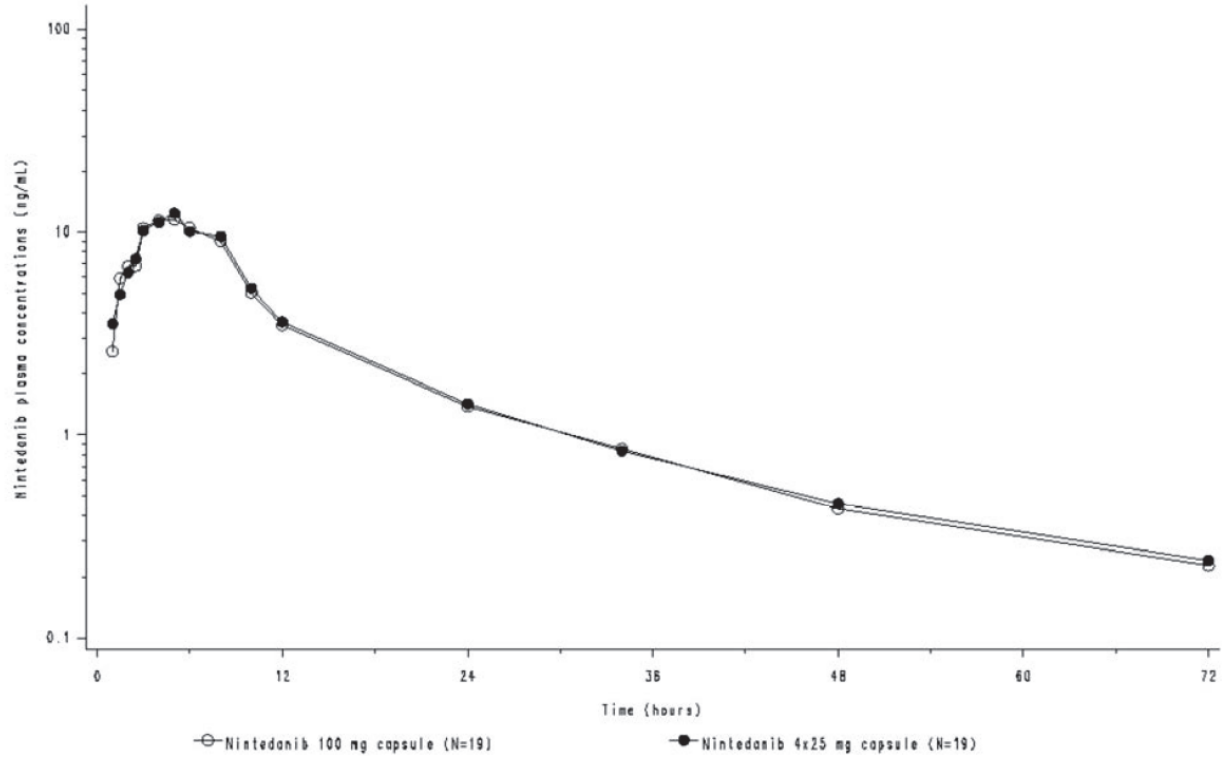
The primary objectives of Study 1199-0337 were the evaluations of PK and safety of nintedanib in children and adolescents with fibrosing ILD. Therefore, Study 1199-0337 was not statistically powered to evaluate efficacy responses. Without incorporating the adult ER relationship as a prior, pediatric data collected in Study 1199-0337 cannot independently establish a reliable ER relationship due to the small sample size. Given the heterogeneity of the clinical features between adult patients with ILD and pediatric patients with ILDs, the reviewer found the ER analysis in pediatric patients insufficient (b) (4)

Was the bioequivalence of the different strengths (b) (4) tested?

Yes. (b) (4)

Study 1199-0463 is an open label, randomized, single-dose, two-period, two-sequence, crossover study in healthy male subjects to evaluate the relative bioavailability of 100 mg nintedanib given as 4 capsules of 25 mg compared to one capsule of 100 mg following oral administration under fed conditions. The primary PK endpoints of this trial were AUC_{0-t} and C_{max} of nintedanib. Secondary endpoint was $AUC_{0-\infty}$ of nintedanib. The mean concentration time profiles are depicted in Figure 4, and the summary of PK parameters are listed in Table 5.

Figure 4: Geometric mean drug plasma concentration-time profiles of nintedanib after single oral administration of 100 mg nintedanib (semi-log scale)



Source: Figure 11.2.1.1: 1 in Clinical Trial Report 1199-0463 (c36734925-01)

Table 5: Comparison of nintedanib PK parameters after single oral administration of 1*100 mg capsule or 4*25 mg capsule

	Nintedanib 1*100 mg capsule (N=19)		Nintedanib 4*25 mg capsule (N=19)	
	gMean	gCV%	gMean	gCV%
C_{max} [ng/mL]	15.2	56.5	15.6	43.2
AUC_{0-tz}[h·ng/mL]	150	40.9	152	33.4
$AUC_{0-\infty}$[h·ng/mL]	157	40.4	160	32.8
t_{max} [h][1]	4.00	(1.00, 8.07)	4.00	(1.00, 8.02)
$t_{1/2}$ [h]	19.8	19.8	20.3	17.9
MRT_{ex} [h]	17.8	18.2	18.2	17.8
CL/F [mL/min]	10600	40.4	10400	32.8
V_z/F [L]	18200	47.6	18400	41.0

1 t_{max} displayed as Median and range (Min, Max)

Source: Table 11.2.1.2: 1 in Clinical Trial Report 1199-0463 (c36734925-01)

The adjusted geometric mean ratios (GMR) and 90% CIs were 100.29% (85.05% to 118.24%) for C_{max}, 98.47% (90.87% to 106.69%) for AUC_{0-t}, and 98.92% (91.35% to 107.12%) for $AUC_{0-\infty}$.

These results indicate similar bioavailability of the two capsule strengths as GMRs were close to 100% and the 90% CIs were clearly within the bioequivalence (BE) limits of 80% to 125%.
No dedicated bioequivalence study was conducted to test the BE between the approved 100 mg and 150 mg dose strength soft gelatin capsules. The normalized exposure comparison was similar between the two strengths based on inter-individual comparison. The geometric mean of dose normalized steady state AUC were 1.15 h.ng/mL/mg and 1.45 h.ng/mL/mg for 100 mg and 150 mg. See Clinical Pharmacology review under the original NDA 205832 submission by Dr. Jianmeng Chen in DARRTS dated 09/14/2014.

What bioanalytical methods are used to assess concentrations of the measured moieties?

The bioanalytical methods used in Study 1199-0337 and Study 1199-0463 are the same bioanalytical methods submitted under the original NDA. See Clinical Pharmacology review under the original NDA 205832 submission by Dr. Jianmeng Chen in DARRTS dated 09/14/2014.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

A single study, study 1199.337, was submitted by the Applicant in support of this submission (Table 6):

Table 6: Study 1199.337 Characteristics

Study	Design	Duration	Treatment	N	Population	Primary Endpoint
1199.337 (inPedILD) *FPFV February 2020* *LPLV May 2022*	Randomized, double-blinded, placebo-controlled, add-on SOC, two-part, parallel group study	24 wks (part A) Variable (part B)	Placebo twice daily Nintedanib twice daily (weight-based)	39	Pediatric ILD patients ages 6-17 years old*	Safety/dose exposure
Abbreviations: FPFV – first patient first visit; LPLV – last patient last visit, SOC – standard-of-care *enrolled patients had progressive disease or severe disease (Fan score >2)						

7.2. Review Strategy

(b) (4) safety and efficacy of nintedanib in pediatric ILD is based on Study 1199.337, referred to hereafter as Study 337. As noted in Table 6, Study 337 was a two-part, randomized, double-blinded, placebo-controlled study in children ages 6 to 17 years old with ILD. In part A, patients were given either nintedanib or placebo on top of SOC for 24 weeks; in part B, all patients completing part A received a variable duration of open-label nintedanib until study termination. The focus of this review is on part A, the blinded controlled portion of Study 337. The variable duration portion (part B) of Study 337 is discussed when relevant.

The FDA Biostatistics confirmed Applicant efficacy analyses (Bayesian and non-Bayesian) and conducted additional analyses when pertinent.

Safety analyses were performed by the clinical reviewer to verify Applicant analyses or initiate other related safety analyses, using Analysis Studio or JMP software. Safety analyses were conducted on the safety population, defined as all randomized patients given at least one dose of study treatment.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 1199.337 Protocol

Study Title

InPedILD®: A double blind, randomized, placebo-controlled trial to evaluate the dose-exposure and safety of nintedanib on top of standard of care for 24 weeks, followed by open label treatment with nintedanib of variable duration, in children and adolescents (6 to 17 year-old) with clinically significant fibrosing Interstitial Lung Disease

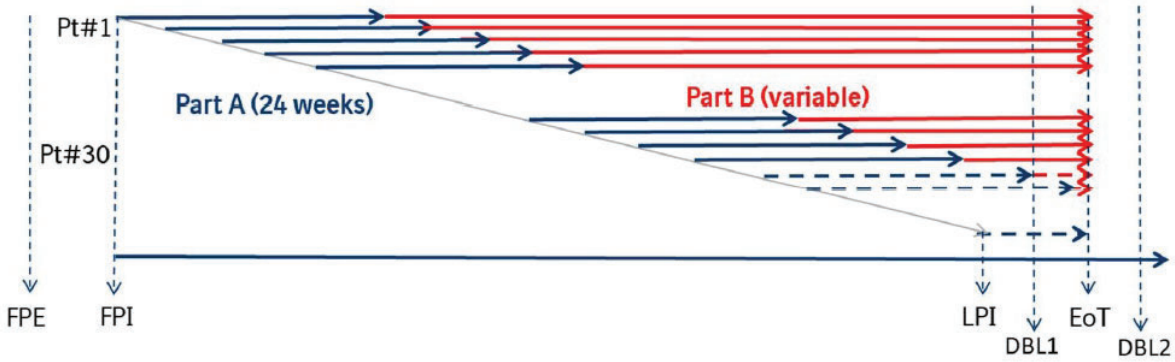
Study Design

Study 1199.337 (Study 337) was a two-part (A and B), multicenter, international, randomized, placebo-controlled, double-blind, parallel-group study to evaluate the dose-exposure and safety of weight-based nintedanib on top of standard-of-care (SOC) to placebo in patients ages 6 to 17 years of age with interstitial lung disease.

Patients were randomized (2:1) after screening (4 weeks) and consent to receive either weight-based nintedanib twice daily or placebo, for 24 weeks. After completion of the 24-week treatment period (part A), patients began open-label nintedanib (part B) at the same dose, until

the end of the trial or premature treatment discontinuation. The duration of part B was variable, dependent on the time when the patient had initiated Study 337 i.e., patients enrolled at the initiation of the trial would have a longer open-label duration than patients enrolled closer to the 30th patient (Figure 5). Patients could enroll in a separate open-label extension study (1199.378) after completion.

Figure 5: Study 1199.337 Schematic



FPE: first patient enrolled; FPI: first patient in (i.e. randomised); LPI: last patient in; EoT: end-of-treatment; DBL1: database lock 1; DBL2: database lock 2
Dashed blue lines represent any patients entered into the trial after the targeted minimum 30 patients.

Source: Study 337 CSR, p.52

Safety oversight was provided by an independent, external safety monitoring committee (SMC), composed of experts in pediatric pulmonology, pediatric endocrinology, pediatric dentistry, and statistics). The SMC met at regular intervals to review PK and safety data. In addition, there was an adjudication committee (composed of a pediatric cardiologist, a pediatric pulmonologist, and an adult cardiologist) to review all deaths and major adverse cardiovascular events (MACE) [non-fatal myocardial infarction, non-fatal stroke, cardiac death].

Once 30 patients (at least 20 adolescents ages 12 to 17) had completed part A, further enrollment stopped, and the database was locked (DBL1). At the time of DBL1, there were 9 patients who had begun the controlled blinded 24-week treatment period before the 30th patient reached 24 weeks. Those patients (as well as patient in the open-label part B) continued dosing while analyses were conducted. Specifically, the PK/safety data from these 30 patients was reviewed to verify adequacy, and a preliminary benefit/risk assessment was performed. Following confirmation of adequate PK/safety data as well as preliminary positive benefit-risk, final database lock occurred (DBL2) and Study 337 was terminated (all dosing stopped for parts A and B). All endpoints were re-analyzed using data collected in the additional time period (between DBL1 and DBL2). This included an additional 9 patients who had blinded controlled part A data (<24 weeks). Patients opting to continue underwent a seamless rollover to Study 1199.378 (open-label extension), or a 4-week follow visit for patients not wishing to continue in the OLE.

Study Endpoints

Primary endpoints:

(1) PK: AUCτ,ss based on sampling at steady state (at week 2 and week 26);
(2) Number (%) of patients with treatment-emergent adverse events at week 24.

Secondary endpoints:

(1) Safety endpoints related to adverse bone, dental, and growth outcomes:
    a. N (%) of patients with treatment-emergent pathological findings of epiphyseal growth plate on imaging at week 24, and week 52*;
    b. N (%) of patients with treatment-emergent pathological findings on dental examination or imaging at week 24, and week 52*;
    c. Change in height, sitting height, leg length from baseline at week 24, week 52*, week 76*, and week 100*.
(2) Number (%) of patients with treatment-emergent adverse events over the whole trial;
(3) Efficacy endpoints:
    a. Change in Forced Vital Capacity (FVC) % predicted from baseline at week 24, and week 52*;
    b. Absolute change from baseline in Pediatric Quality of Life Questionnaire™ (PedsQL™) at week 24, and week 52*;
    c. Change in oxygen saturation (SpO2) on room air at rest from baseline at week 24, and week 52*;
    d. Change in 6-min walk distance from baseline at week 24, and week 52*;
    e. Time to first respiratory-related hospitalization over the whole trial;
    f. Time to first acute Interstitial Lung Disease (ILD) exacerbation or death over the whole trial;
    g. Time to death over the whole trial.
(4) Patient acceptability of capsules:
    a. Patient acceptability based on the size of capsules at week 24;
    b. Patient acceptability based on the number of capsules at week 24;

*Week 52 comparisons between treatment arms were for patients randomized to placebo who switched to open-label (OL) after Week 24 (placebo/nintedanib) vs. patients randomized to nintedanib who continued with OL after Week 24 (nintedanib/nintedanib).

Additional endpoints included further timepoints and categorical analyses based on FVC, Peds QL, SpO2, and quantitative changes in Fan scores, heigh, weight, BMI.

Statistical Analysis Plan

Analysis sets:

(1) Randomized set: This patient set includes all randomized patients, whether treated or not.
(2) Treated set: The Treated Set (TS) consists of patients who were randomized to a treatment group and receive at least one dose of study medication.
(3) Pharmacokinetic parameter analysis set (PKS): This set includes all patients in the treated set (TS) who provided at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the CTP Sec. 7.2.1.). Thus, a patient was included in the PKS, even if he/she contributed only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters were based on the PKS.

Analyses for PK endpoints were based on the PKS. All other analyses were based on the TS except for disposition.

Sample size calculation:
The main objective was assessed by calculating descriptive statistics for safety endpoints and by exploratory PK analyses. The target sample size of a minimum of 30 patients was based on the sample size estimation for the evaluation of the primary endpoint of PK and trial feasibility evaluation.

Primary PK/safety analysis:
See Section 6 *Clinical Pharmacology* for details regarding the PK analyses. See Section 8.2 *Review of Safety* for details regarding safety analyses.

Key secondary endpoints (efficacy) analysis models:

1. Continuous change from baseline endpoints: The continuous secondary endpoint analysis was based on the TS (according to randomized treatment), using available data from all visits (after time-windowing) from Part A and Part B and the estimate and contrast between treatments at the applicable endpoint visits was used. The analysis of continuous secondary endpoints was a restricted maximum likelihood (REML) based approach using a Mixed effect Model for Repeated Measures (MMRM). The analysis included the fixed, categorical effects of treatment at each visit, age-group and the fixed continuous effects of baseline at each visit. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors. Significance tests were based on least-squares means (two-sided 95% confidence intervals were presented). The MMRM used for the analysis of continuous secondary endpoints allowed for missing data, assuming

they are missing at random. If no FVC measurement prior to first trial drug intake was available, the baseline FVC value was imputed with the earliest FVC value obtained after (but on the same day as) the first trial drug intake. The primary treatment comparison was the contrast between treatments at the endpoint visit. Additionally, a descriptive analysis for all time points was done.

2. Time-to-event endpoints: Separate Kaplan-Meier plots were presented by randomized treatment group and overall (total group) for time-to-event endpoints. Kaplan-Meier estimates and confidence intervals (using the Greenwood variance formula) for the cumulated time-to-event rate were calculated at 24 weeks and at 52 weeks. Q1, median and Q3 of the time to event were presented, if reached. No statistical test was performed. Missing or incomplete data were managed by standard survival analysis techniques (i.e. censoring). A missing or incomplete date of death was imputed/completed that the derived date was the earliest possible date which is on or after date of onset of the fatal AE, and on or after treatment start (in case this AE is treatment-emergent), and on or after derived date of last contact.

3. Categorical endpoints, safety and tolerability endpoints: Only descriptive analyses in the form of frequency tables were performed. In the analyses of the binary endpoints, multiple imputation was used to handle missing data at week 24. For week 52 and later, data were not imputed and only observed values were used.

4. Integration of prior knowledge on the treatment effect on FVC % predicted in adults in a supporting efficacy analysis within pediatric patients by use of a Bayesian approach with a prior derived from adults: Across all phase 3 trials of nintedanib in different adult ILD indications, analyses of the primary endpoint, annual rate of decline in FVC (mL/year), have shown consistent relative treatment effects of nintedanib on reducing the rate of decline in FVC over 52 weeks across the spectrum of fibrosing ILDs. These analyses provide evidence on the consistency of the effect of nintedanib in adult patients with a broad range of ILD diagnoses.

   However, the results of these analyses cannot be directly used to construct an informative prior distribution on the treatment effect for the analysis of 1199.337 via a Bayesian borrowing approach. On the one hand, the double-blind period in 1199.337 is only 24 weeks. On the other hand, FVC measured in mL is not expected to decrease in pediatric patients as the lung function in children is increasing over time. Therefore, the calculation and estimation of relative treatment effects as done for the different adult ILD indications in P21-03717 was not justified in pediatric patients.

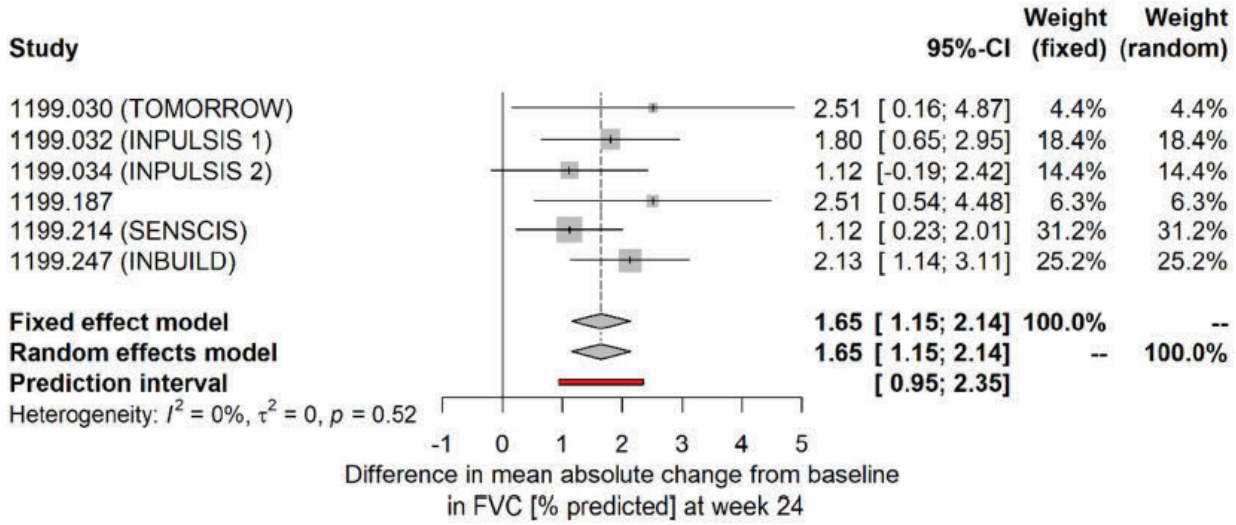
   Instead, a meta-analysis across all placebo-controlled trials from the nintedanib development programs in IPF, SSc-ILD and PF-ILD with double-blind periods of at least 24 weeks had been performed based on the estimated treatment effect on FVC % predicted at 24 weeks, with the aim to derive a meta-analytic-predictive (MAP) prior. As

FVC % predicted accounts for differences in age and height, it was expected to be less affected by growth and better suited for extrapolation from adult to pediatric patients than FVC values in mL. Based on the resulting MAP prior, the observed treatment effects in adult patients with different types of ILDs could be incorporated in the analysis of pediatric patients in trial 1199.337 via a Bayesian borrowing approach.

- Prior derivation

The nintedanib development program assessed changes in FVC % predicted across clinical trials with a duration of at least 24 weeks in adult patients with SSc-ILD, IPF and other fibrosing interstitial lung disease with progressive phenotype. Figure 6 shows the result of the meta-analysis of change from baseline in FVC % predicted at 24 weeks. The treatment effect was consistent and there was no indication of heterogeneity across the trials.

Figure 6: Historical data – meta-analysis on mean absolute change from baseline in FVC [% predicted] at week 24



Source: Study 337 SAP Figure 7.5.2.4:1, p.50

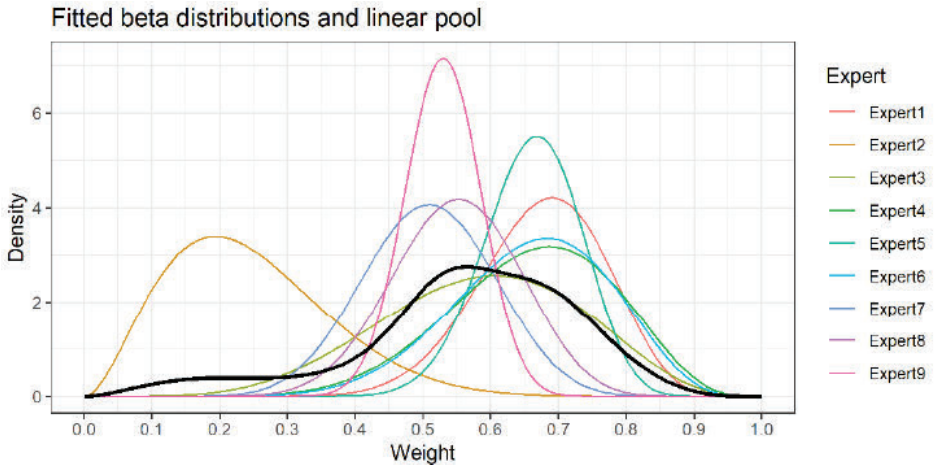
Based on these results, an informative prior was derived using the concept of MAP priors. This prior was then approximated using a mixture distribution. The approximation of the informative MAP prior yielded a 2-component normal mixture distribution. Weights, means and standard deviations were 0.76, 1.66 and 0.39, respectively, for the first component, and 0.24, 1.80 and 1.06, respectively, for the second component. A Bayesian dynamic borrowing approach was applied, as proposed by Best et al. (2021). This approach used a robust mixture prior distribution consisting of an informative component (implying a treatment effect) and a weakly informative component with a distribution centered on a mean of zero (implying no treatment effect). The informative component was represented by the derived MAP prior using the

adult data. The weight of this component in the prior distribution reflects the degree of belief in its validity for the pediatric trial data.

- A formal prior elicitation

The Applicant conducted a formal prior elicitation workshop on 9-10 September 2021 to determine a sensible weight *w* of the informative component of the robust MAP prior for pre-specification. The elicitation exercise followed the Sheffield Elicitation Framework and recommendations in the literature (Gosling 2018, Dallow 2018). Nine international clinical experts in pediatric and adult pulmonology participated. The elicitation task for the experts was to provide a judgement on the most appropriate weight of the informative component based on their belief in the similarity of diseases between children and adults, and the consistency of the treatment effect (given existing pre-clinical and clinical evidence, as well as personal experience and opinion), as well as statistical considerations (consequences for inference as seen in hypothetical tipping point analyses and operating characteristics). The elicitation was performed using the 'roulette' method (with 10 chips to be allocated to 10 bins) to generate histogram-like data on the experts' judgements (including their uncertainty) concerning the weight parameter (Gosling 2018, Dallow 2018). Importantly, all experts felt able to perform the elicitation task. Figure 7 shows beta densities fitted to the raw data provided by the experts and a pooled distribution of all judgements (black line). The mean of the pooled distribution was 0.56, the median was 0.58, the first quartile was 0.48 and the third quartile was 0.68. Based on these results from the expert elicitation, the Applicant suggested a primary weight of the informative component of the robust MAP prior distribution equal to 0.56, i.e., the mean of the expert's judgements, in the supportive efficacy analysis, along with a one-sided 90% evidence level.

Figure 7: Results from expert elicitation on the weight of the informative component



Source: Response to Information Request (dated Aug 18, 2023) Appendix 1 Figure 3, p.6

A tipping point analysis was carried out to identify how much prior weight needs to be placed on evidence from trials in adults to establish efficacy in the pediatric population. Different weights ranging from 0% to 100% was used. An one-sided evidence level of 90% was targeted and a prior weight of 56% (weight was determined in a formal prior elicitation workshop with medical experts) on the adult data was considered in the main analysis, but the descriptive statistics (including median and 2.5%, 5%, 25%, 75%, 95% and 97.5% quantiles) of the posterior distributions used for the tipping analysis was reported.

Multiplicity adjustment:

No adjustment for multiplicity was made. Any p-value presented was considered nominal in nature.

Protocol Amendments

There were two global protocol amendments, dated June 19, 2020 (Amendment 1) and June 14, 2021 (Amendment 2).

As part of Amendment 1, selected personnel involved in PK analyses were unblinded to conduct interim PK evaluation at Week 2 post-dose (FDA recommendation) to ensure appropriate systemic exposure. Other changes were minimal.

As part of Amendment 2, changes were related to follow-up laboratory testing, end-of-trial procedures (open label rollover, repeat safety testing, PK sampling repeat), COVID-19 pandemic risk mitigation measures, DBL1 PK assessment clarifications, weight loss safety measures, bone and dental AE related instructions (designations as AESI, treatment interruption instructions), and other administrative changes.

Overall, all protocol amendments were reviewed by the review team, and the review team believes that changes are unlikely to impact the overall conclusions.

8.1.2. Study Results

Compliance with Good Clinical Practices

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted and verifies that no compensation is linked to study outcome. The principal investigators (PIs) did not disclose any proprietary interest to the sponsor; the Applicant notes that no PIs (or sub-investigators) held financial interests requiring disclosure. See section 19.2 for further details.

Patient Disposition

A total of 87 patients were screened across 43 sites in 21 countries (25 sites in Europe, 11 in North America, and 7 in the rest of the world). Of these 87 patients, 39 patients were randomized and treated. The most common screen failure reason was failure to meet inclusion and exclusion criteria (45 of the 48 screen failures).

At the time of DBL2, over 85% of patients in each arm had completed the 24 weeks of study. The most common reason for not completing the study in each arm was related to the administrative end to the trial before these patients had reached Week 24. More patients in the nintedanib arm discontinued study treatment (mostly due to AEs); otherwise, patient

disposition was fairly balanced between arms. Key patient disposition information is summarized in Table 7.

Table 7: Disposition, up to DBL2

	Placebo n(%)	**Nintedanib n(%)**
Screened	87	
Randomized	13 (100)	26 (100)
Completed 24 weeks of Treatment*	11 (85)	21 (81)
Treatment discontinuation before 24 weeks of Treatment	2 (15)	5 (19)
Administrative end of trial	2 (15)	2 (8)
Premature study drug discontinuation	0	3 (12)
Adverse event	0	2 (8)
Other	0	1 (4)
Completed 24 weeks of Study**	11 (85)	23 (88)
Did not complete 24 weeks of Study	2 (15)	3 (12)
Administrative end of trial	2 (15)	3 (12)

*all patients who completed 24 weeks of treatment started open-label treatment in part B
** all patients who completed the planned observation period in the 24 weeks of double-blinded period (last visit or vital status 'alive' recorded in or after planned time window for Week 24 visit (on or after Day 166)

Source: CSR Table 10:3, p.143; FDA Biostatistical team confirmed

Protocol Violations/Deviations

No protocol deviations (PD) led to exclusion of patients from the analysis. The most common important protocol deviations were related to safety procedure/SAE reporting, trial medication administration, and eligibility criteria adherence. Overall, there were more nintedanib patients with PDs during the blinded controlled treatment period. Table 8 summarizes the important protocol deviations.

Table 8: Protocol Deviations

Protocol Deviation	Placebo N=13 n(%)	Nintedanib N=26 n(%)
Patients with any protocol deviation	1 (8)	11 (42)
Safety procedure/SAE reporting	1 (8)	7 (27)
Pregnancy testing too infrequent	1 (8)	2 (8)
Consecutive x-ray time period too short	0	2 (8)
Image acquisition guideline not followed for imaging (minimum radiation)	0	3 (12)
Tral medication administration	0	3(12)
Treatment interruption error	0	1 (4)
Dosing error (low dose)	0	1 (4)
Dosing frequency error (QD vs. BID)	0	1 (4)
Eligibility criteria adherence	0	3 (12)
HRCT criteria not met	0	2 (8)
FVC criteria error (visit 2 lower bound)	0	1 (4)

Source: CSR Table 10:7, p.150

While there are numerical differences between arms for PDs (Table 6), several PDs would be expected to have no impact given that follow-up assessments could account for any deviation from the routine (e.g., an early imaging assessment or a delayed pregnancy test). In addition, the protocol deviations were not disproportionately concentrated in one category (such as medication administration or safety procedures). When considering data from the whole trial (including the open label variable duration portion), there were no new nintedanib/nintedanib patients with PDs, and two additional placebo patients (placebo/nintedanib 3 [23%] vs. nintedanib/nintedanib 11 [42%]).

These PDs are unlikely to have had a notable impact on the overall analysis of safety and efficacy.

Demographic and Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

As shown in Table 9, the majority of patients were adolescents, Caucasian, and female. All Black and Asian patients were randomized to the nintedanib treatment arm with none in the placebo arm. Aside from this, there were no other notable demographic differences between treatment arms. It is also worth noting that the study population had lower than expected BMIs when adjusted for age (BMI-for-age z-score at baseline was -0.6, not shown in Table).

With regard to baseline characteristics, patients had their underlying ILD diagnosis for at least 5 years. The most common underlying diagnoses were surfactant protein deficiency and SSc. Most patients had severe and/or progressive disease, with progression based mostly on worsening imaging. As expected for an ILD study population, pulmonary function tests showed decreased FVC and diffusion capacities, in the 50-60% range.

Table 9: Demographic and Baseline Characteristics

Patient Characteristic	Placebo N=13	Nintedanib N=26	Total N=39
Demographics			
Male (# of patients, %)	5 (39)	10 (39)	15 (39)
Race (# of patients, %)			
White	12 (92)	19 (73)	31 (80)
Black	0	3 (12)	3 (8)
Asian	0	2 (8)	2 (5)
Mean Age (SD)	13 (3)	13 (4)	13 (3)
Mean Weight (SD)	45kg (22)	41 (16)	42kg (18)
Mean Standing Height (SD)	148cm (16)	147cm (17)	148cm (17)
Mean BMI (SD)	19.2 (6.4)	18.2 (3.8)	18.5 (4.8)
Disease and Baseline Characteristics			
Time since ILD diagnosis (mean, SD)	7 (5)	5 (5)	6 (5)
Underlying ILD diagnosis (# of patients, %)			
Surfactant protein deficiency	5 (39)	7 (27)	12 (31)
Other childhood ILD*	3 (23)	7 (27)	10 (26)
SSc	3 (23)	4 (15)	7 (18)
Toxic/radiation/drug-induced pneumonitis	1 (8)	3 (12)	4 (10)
Other autoimmune (DM, JIA, JRA)	1 (8)	2 (8)	3 (8)
Chronic hypersensitivity pneumonitis	0	2 (8)	2 (5)
Post-HSCT fibrosis	0	1 (4)	1 (3)
Fan score			

≥3 (# of patients, %)	6 (46)	17 (65)	23 (59)
Mean (SD)	3 (1)	3 (1)	3 (1)
Clinical progression over time criteria (# of patients, %)			
FVC decline 5-10% + worsening symptoms	3 (23)	6 (23)	9 (23)
FVC decline ≥ 10%	3 (23)	5 (19)	8 (21)
Increased fibrosis on imaging	11 (85)	14 (54)	25 (64)
Other measures of clinical worsening**	3 (23)	9 (35)	12 (31)
Baseline testing			
FVC %predicted (SD)	63 (23)	58 (22)	59 (22)
DLCO %predicted (SD)	63 (11)	53 (27)	56 (23)
6MW distance, meters (m) (SD)	371 (136)	390 (134)	384 (133)
Chronic glucocorticoid therapy received or ongoing (# of patients, %)	7 (54)	20 (77)	27 (69)
Abbreviations: JIA – juvenile idiopathic arthritis; JRA – juvenile rheumatoid arthritis; SSc – systemic sclerosis; DM – dermatomyositis; ILD – interstitial lung disease; HSCT -hematopoietic stem cell transplant *Other childhood ILD included the following: COPA syndrome, bronchiolitis obliterans, unspecified ILDs or unspecified fibrosis, emphysema, pulmonary alveolar proteinosis, post lung transplant fibrosis, DIP, Kartagener syndrome, covid, influenza, chronic bronchitis, PPFE, NSIP, lupus related ILD, follicular bronchiolitis, BPD, fibrosing alveolitis, ILD related to undifferentiated CTD, sting associated vasculopathy *(Source Table 9.5:1 from Appendix 16.1.9 from Applicant submission)* **Other measures of clinical worsening included the following: worsening diffusion capacity, increasing oxygen requirements, worsening exercise tolerance, lower oxygen saturations, initiation of supplementary oxygen, need for non-invasive ventilation during sleep (Source: ADSL database review by FDA review team)			

Source: Study 337 CSR Tables 10:10-13

It is worth noting that the study population in Study 337 was notably different than an adult ILD population. Besides the obvious differences in age, the study population in Study 337 had a large proportion of patients with genetic/familial conditions (e.g., surfactant protein C deficiency, COPA syndrome), which was not similarly represented in the adult PPF trial (1199.247, INBUILD). As such, this difference in the nature of the underlying ILDs enrolled in Study 337 as compared to the adult ILDs enrolled in the INBUILD trial presents further challenges to the ability to correlate/extrapolate benefit-risk between adult and pediatric ILDs. This is further discussed in section 8.1.4.

In addition, there were patients with abnormal bone imaging and dental imaging at baseline. While there were few patients with baseline abnormal bone imaging of the epiphyseal growth plate (2 placebo patients [15%], 1 nintedanib patient [4%]), there were frequent baseline dental abnormalities (e.g., pathological dental exam findings at baseline: placebo 7 [54%] vs. nintedanib 12 [46%]; patients with impacted permanent teeth at baseline: placebo 5 [39%] vs. nintedanib 13 [50%]). It is unclear if the frequent use of chronic corticosteroids played a role in the baseline dental observations.

Overall, given the small sample size, one would expect some degree of numerical differences between treatment arms at baseline for various study population characteristics (e.g., race,). It is unlikely that these differences would account for sizeable differences between arms for the safety and efficacy results that will be discussed in the next sections of the review.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance, as measured by remaining trial medications from empty packages brought at clinic visits, was between 80-120% for all patients in both treatment arms, both during the 24-week controlled treatment period (mean compliance ~ 98% in both arms) as well as during the entire trial (mean compliance ≥ 97% in both arms).

Concomitant medications were used by all patients, which is not unexpected given the underlying conditions being studied. The most common baseline therapies were hydroxychloroquine (31%), azithromycin (28%), mycophenolate mofetil (21%), and prednisone (18%) [corticosteroids were used by ~33%], and the most common class of medications that patients were on at baseline was immunosuppressants (82%). Using a threshold for potential relevance of ≥20% between arms (given the small sample size), there were two medications that were more commonly used at baseline by placebo patients: hydroxychloroquine (46% placebo vs. 23%) and salbutamol (39% placebo vs. 4%). When considering all concomitant medications (baseline + medications added during the study period), similar observations were present: few patients changed baseline therapies or started new medications during the controlled treatment period. *Source: Tables 10:20 and 10:22 CSR Study 337*

It is worth noting that more patients in the placebo arm were vaccinated against COVID-19 (31% vs. 12%). Furthermore, there were no patients in the nintedanib arm and 1 patient in the placebo arm who had reported having had COVID-19 prior to trial entry. These factors may have impacted the observed safety findings in which COVID-19 occurred more often in nintedanib patients (see Table 11).

In summary, there were minor differences between treatment arms for usage of certain medications (e.g., salbutamol) which is not expected to impact safety and efficacy outcomes appreciably. While the potential for the difference in hydroxychloroquine usage was considered by the review team as a potential confounder (based on case reports of a stabilizing effect[6] [7]), it was noted that the eligibility criteria for Study 337 were such that severe and/or progressive disease would be necessary for study entry, negating any potential for this to be a confounder.

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[6] Manali ED, Legendre M, Nathan N, et al. Bi-allelic missense ABCA3 mutations in a patient with childhood ILD who reached adulthood. ERJ Open Res 2019; 5: 00066-2019 [https://doi.org/10.1183/23120541.00066-2019].
[7] Nikolaidou, P.; Charocopos, E.; Anagnostopoulos, G.; Lazopoulou, D.; Kairis, M.; Lourida, A.; Tzoumakas, K.; Tsiligiannis, T. Cellular Interstitial Pneumonitis in Children: Response to Hydroxychloroquine Treatment in Two Cases. Pediatr. Asthma Allergy Immunol. 2003, 16, 45–51.

Lastly, treatment compliance was high and balanced across arms. As such, concomitant medications and treatment compliance are unlikely to have impacted efficacy outcomes.

Efficacy Results – Primary Endpoint

The primary endpoint in Study 337 was PK/safety. Efficacy endpoints were secondary and exploratory.

Data Quality and Integrity

There were no data quality or integrity issues noted.

Efficacy Results – Secondary and other relevant endpoints

Efficacy endpoints in Study 337 were secondary and exploratory endpoints. These included the following:

1. Change from baseline in FVC % predicted at Weeks 24 and 52
2. Absolute change from baseline in Pediatric Quality of Life Questionnaire (PedsQL) at Weeks 24 and 52
3. Change from baseline in oxygen saturation (SpO2) on room air at rest at Weeks 24 and 52
4. Change from baseline in 6MWT at Weeks 24 and 52

In addition to the planned primary analyses, Bayesian analyses were conducted to aid in the interpretation of efficacy.

Other efficacy endpoints included patient acceptability based on the size and number of capsules at Week 24, time to first respiratory-related hospitalization over the whole trial, time to first acute ILD exacerbation or death over the whole trial, time to death over the whole trial, and analyses based on threshold changes in FVC % predicted, PedsQL, SpO2, hospitalization duration, and missed school days.

All efficacy analyses were based on controlled data up to DBL2. Results from analyses for Week 52 time points are not discussed as this includes uncontrolled data.

Result for the efficacy endpoints listed in #1 to #4 above (restricted to Week 24, up to DBL2) are shown in Table 10.

Table 10: Efficacy Endpoints, Week 24, ITT/Treated set, up to DBL2

Parameter	Nintedanib (N = 26)	Placebo (N = 13)	Treatment difference
Change from baseline in FVC % predicted, 95% CI	0.3 [-2.4, 3.0]	-0.9 [-4.6,2.8]	1.2 [-3.4, 5.8]
Change from baseline in oxygen saturation (SpO2) on room air at rest, 95% CI	0.1% [-1.5, 1.6]	-2.3% [-4.5, -0.04]	2.3% [-0.4, 5.0]
Change from baseline in 6MWT, meters, 95% CI	17.6 [-15.9, 51.2]	10.5 [-36.0, 57.0]	7.1 [-50.3, 64.5]
Absolute change from baseline in Pediatric Quality of Life Questionnaire (PedsQL) total score (parent assessment), 95% CI	5.5 [0.4, 10.6]	5.6 [-1.5, 12.7]	-0.1 [-9.0, 8.7]
Absolute change from baseline in Pediatric Quality of Life Questionnaire (PedsQL) total score (patient assessment), 95% CI	5.5 [-0.1, 11.0]	6.5 [2.5, 10.5]	1.0 [-5.9, 7.9]

Values are adjusted means (95% CI) based on MMRM with fixed categorical effects of (randomised) treatment at each visit, age-group and the fixed continuous effects of baseline at each visit, and random effect for patient. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within–patient measurements. Adjusted mean was based on all analyzed patients in the model (not only on patients with a measurement both at baseline and at the respective visit)

Source: CSR Table 11:2 p.192

As noted in Table 10 above, FVC results do not provide clear support for efficacy as the 95% confidence intervals for the FVC analysis are wide and include the null value. Moreover, the point estimate is modest. In addition to FVC, other efficacy endpoints were also evaluated.

Because results from the SpO2, 6MWT, and PedsQL show modest changes, and the minimum clinically important difference (MCID) is unknown in this study population, they also do not provide support for efficacy. In addition to these efficacy endpoints, assessments for hospitalizations, exacerbations, and death were performed to further evaluate efficacy.

While there were no deaths, there were 2 hospitalizations, both in nintedanib-treated patients, one of which was reported as an exacerbation. Given the low frequency of events, it is difficult to draw conclusions. However, the exacerbation/hospitalization data does not support a favorable exacerbation or hospitalization-related treatment effect for nintedanib over placebo.

Based on the above, there was no clear support for efficacy for nintedanib. However, because it was recognized that Study 337 was not powered for efficacy (due to feasibility in the setting of a rare disease) as well as the possibility that the adult condition (PPF) may have similarities to the pediatric condition (pediatric ILD), Bayesian analyses for FVC had been pre-specified to aid in the interpretation of efficacy.

The Bayesian analyses for FVC will be discussed to understand the manner in which knowledge of nintedanib's treatment effect in adults would be used to inform the treatment effect in patients ages 6 to 17 years old.

As pre-specified (see section 8.1.1 *Statistical Analysis Plan*), a Bayesian dynamic borrowing approach was applied to the analysis for FVC % predicted at Week 24. Information from nintedanib's clinical experience in adults with ILD (including IPF, SSc-ILD, PPF) was used to inform the treatment effect in pediatrics, and key opinion leader (KOL) input was solicited to determine a pre-specified prior weight.

Using a pre-specified weight (0.56) of an informative component in the previously determined robust meta-analytic predictive prior (from nintedanib's known treatment effect in adults with IPF, SSc-ILD, and PPF) the Bayesian analysis of the change from baseline FVC % predicted at Week 24 was 1.63% (80% credible interval 0.78, 2.37). While results for the Bayesian analyses for FVC % predicted Week 24 using the 80% credible interval exclude the null value, results based on a more commonly used 95% credible interval (-0.69, 3.40) do not exclude the null value, and thus fail to achieve a one-sided evidence level of 97.5%, which is typically used for primary efficacy analyses. Note that the lower pre-specified credible interval (80%) was based solely on the rarity of the disease and difficulties with enrollment. Results for various credible intervals are shown in Table 11.

Table 11: Bayesian Analyses for FVC % predicted, Week 24, Treated Set

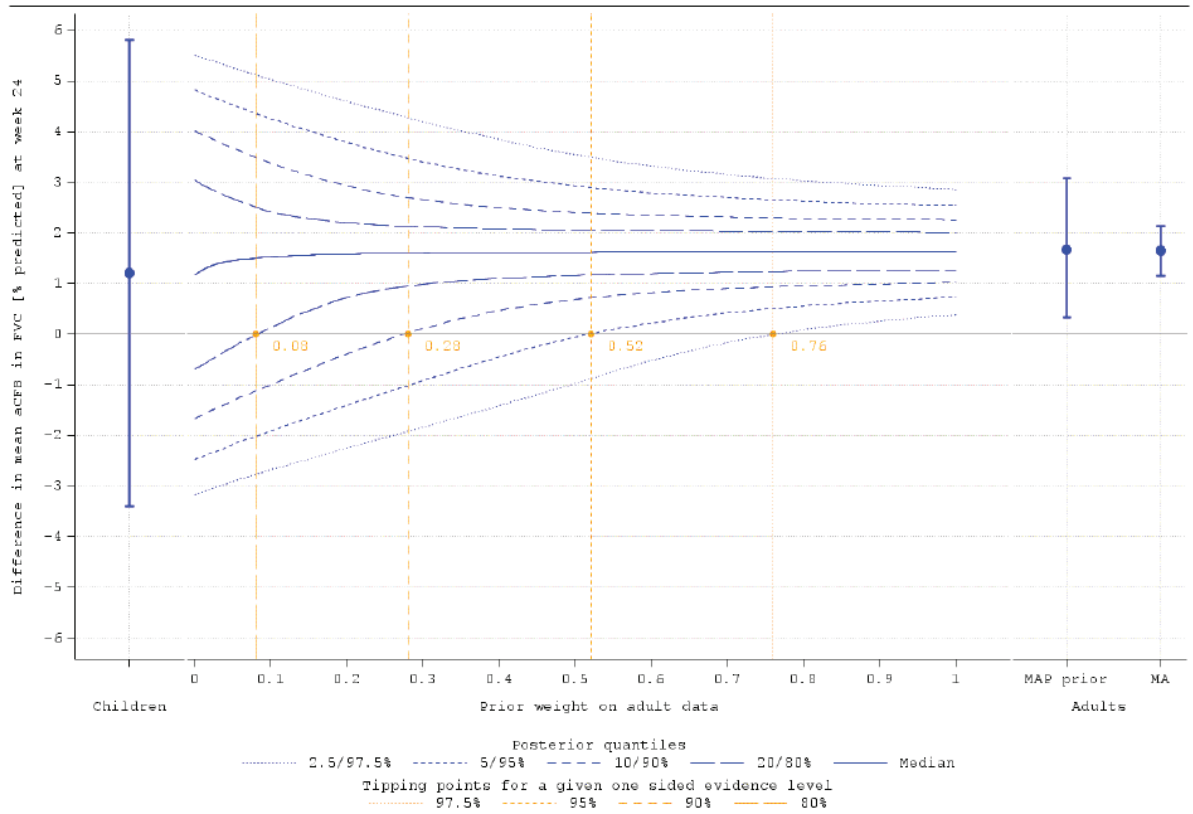
Posterior Credible Interval (CrI)	Posterior Median of Treatment Difference (Nintedanib vs Placebo) in Mean Absolute Change (Credible interval)
80% CrI	1.63 (0.78, 2.37)
90% CrI	1.63 (0.12, 2,84)
95% CrI	1.63 (-0.69, 3.40)

A Bayesian dynamic borrowing approach was applied to the treatment effect of nintedanib on FVC % predicted at Week 24 using a prior derived from adults (using the pre-specified prior weight of 56%), and combining it with the analysis of pediatric data from trial 1199-0337. Descriptive statistics (including median and 2.5%, 5%, 10%, 90%, 95% and 97.5% quantiles) of the posterior distributions were used to derive credible intervals. The posterior probability of nintedanib being superior to placebo was 95.54%.

Source: CSR Table 12.1.1.5, p.2086

The Bayesian analyses for FVC% predicted at Week 24 were further assessed for different prior weights ranging from 0 (0%) to 1 (100%) in the pre-specified tipping point analysis. The resulting tipping points are displayed in Figure 8. The 80% credible intervals (posterior quantiles 10/90%) indicate that the targeted 1-sided evidence level of 90% was achieved with the prior weight of 28% on the adult data, which is below the pre-specified prior weight of 56%. However, the 95% credible intervals (posterior quantiles 2.5/97.5%) indicate that it requires a prior weight of 76%, which is above the pre-specified prior weight of 56%, to achieve one-sided evidence of 97.5% (the posterior probability that nintedanib is superior to placebo being at least 97.5%).

Figure 8: Tipping Point Analysis for Absolute Change from Baseline in FVC% predicted at Week 24 - Treated Set



Source: CSR Figure 11:6, p.200

As the Bayesian weight on the adults priors was not equivalent to the actual degree of borrowing, additional analyses were performed. To quantify the actual degree of borrowing, the Applicant calculated the effective sample size of the proposed robust MAP prior using the expected-local-information-ratio (ELIR) method for various weights (including the pre-specified 56% weight). These are shown in Table 12.

Table 12: Bayesian Weights, Credible Intervals, Borrowed Adult data

Bayesian Weight on Adults in Prior	**Difference in Mean Absolute Change**			**Probability of Difference >0**	**Number of Borrowed Adult Data[1]**	**Percentage of Total Data from Adults[2]**
	Posterior Median	80% Credible Interval	95% Credible Interval			
0	1.17	(-1.67, 4.02)	(-3.18, 5.52)	70.15%	0	0%
0.1	1.53	(-0.99, 3.38)	(-2.68, 5.03)	81.48%	40	50%
0.3	1.61	(0.11, 2.65)	(-1.84, 4.20)	90.73%	173	81%
0.5	1.62	(0.69, 2.06)	(-0.97, 3.55)	94.75%	323	89%
0.56[3]	1.63	(0.78, 2.37)	(-0.69, 3.40)	95.54%	370	90%
0.7	1.63	(0.90, 2.31)	(-0.17, 3.32)	96.99%	482	92%
0.9	1.64	(0.99, 2.27)	(0.26, 2.94)	98.43%	647	94%
1.0	1.64	(1.02, 2.25)	(0.39, 2.87)	98.96%	>725	>94%

[1] The number of borrowed adult data for each weight was calculated by the ELIR method (effective sample size of robust MAP prior).
[2] The percentage of total data from adults for each weight was calculated as borrowed adult data ÷ (borrowed adult data + pediatric data (39) +1)
3 The Bayesian weight on Adults in Prior of 0.56 was the prespecified weight in the Statistical Analysis Plan
Source: FDA Statistical Reviewer

Based on the above, the FDA review team noted concerns with the efficacy results:

1. A modest FVC treatment effect was noted, regardless of the credible interval selected or the weight applied, with a range of approximately 1.2% to 1.7%.
2. A high degree of adult data borrowing (90%) was needed to achieve results where the 80% credible interval excluded the null for the pre-specified weight of 0.56. Even at weights as low as 0.3, over 80% of total data is obtained from adults. To achieve results where the 95% credible interval would exclude the null, the weight on adults in the prior would have to be greater than 0.7 and it would require borrowing even larger amounts of adult data relative to the collected pediatric data (>92%).
3. By using a lower level of credible interval (80% vs. 95%), as used by the Applicant due to the rarity of the disease/feasibility, there is added uncertainty introduced with regard to the true treatment effect.

In summary, based on the efficacy data from Study 337, there is considerable uncertainty regarding the treatment effect of nintedanib in pediatric ILD patients. While there is a possibility of a modest FVC treatment effect (1.2 to 1.7 FVC %predicted) for nintedanib in pediatric ILD patients based on Bayesian analyses, this is uncertain as it relies on a large degree of borrowing of adult data (>90%). When fewer adult data are borrowed (e.g., 50%), most credible intervals (e.g. 80% and 95%) include the null value. Using the prespecified weight of

0.56, for the 80% credible interval to exclude the null, the degree of adult borrowing was 90%. We also note for the 95% credible interval to exclude the null, which is typically used for primary efficacy analyses, adult data borrowing of 94% would be required. To justify such an amount of actual borrowing, the adult and pediatric diseases would have to be essentially identical. While there may be some similarity in the adult and pediatric diseases, it is unlikely that the similarity is to the extent that borrowing of such large amounts of adult data is scientifically justified. Therefore, the FVC results using a Bayesian approach do not provide robust support for efficacy.

Dose/Dose Response

Dose response was not explored in this submission.

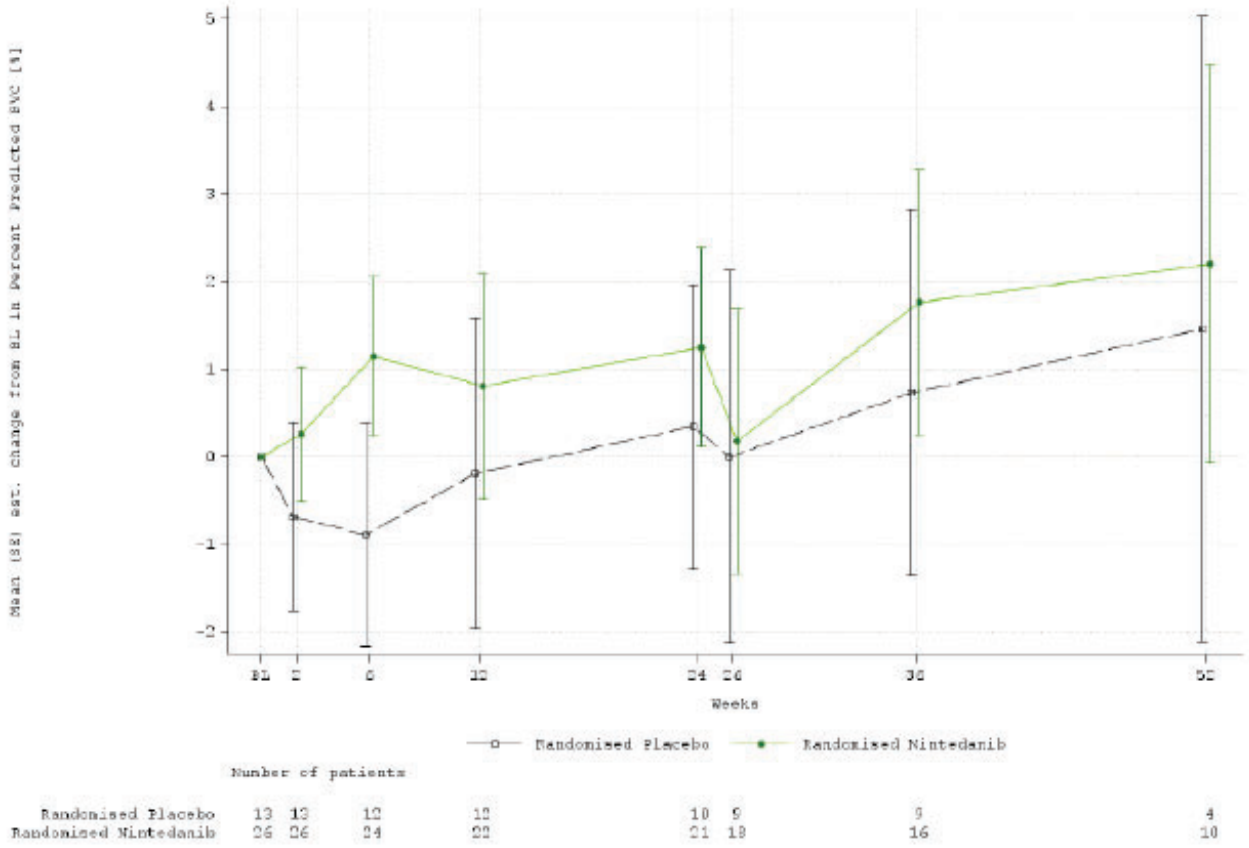
Study 337 used a weight-based allometric scaling system to determine dosing for pediatric patients. Because there was only one dosing arm, there was no ability to determine dose response. Given the rarity of the disease, dose exploration may be challenging in this pediatric population. See Section 6 *Clinical Pharmacology* for further details.

Durability of Response

To evaluate for durability of response, change from baseline in FVC was assessed throughout Study 337 Part A (24-week blinded controlled period) and part B (open-label uncontrolled variable duration). Because of the uncontrolled nature of the data from the variable duration portion, durability of response can only be assessed over the 24-week part A (FVC curves restricted to left portion of Figure 9, up to week 24 on the x-axis).

The difference between placebo and nintedanib groups did not appear to diminish over the 24-week control period. However, given the small sample size, standard error bars are widely overlapping.

Figure 9: FVC over time, controlled and uncontrolled data



In conclusion, based on the small sample size and short controlled period duration of 24 weeks (relative to 52 weeks typically used for FVC endpoints), no conclusions can be drawn regarding durability of treatment effect.

Persistence of Effect

Persistence of efficacy after treatment discontinuation was not separately evaluated. Thus, an analysis of spirometry or other efficacy endpoints in patients discontinuing treatment in a systematic fashion cannot be performed. A persistence of treatment effect for nintedanib is not expected based on its mechanism of action and known pharmacology.

8.1.3. Integrated Assessment of Effectiveness

The efficacy of nintedanib in pediatric ILD patients ages 6 to 17 is uncertain, and at best of a modest effect size.

In Study 337, there was no support for efficacy from FVC analyses (frequentist statistical methodology), nor did non-FVC based efficacy endpoints provide support for a treatment effect. Results from FVC based efficacy analyses demonstrated modest point estimates of a treatment effect with 95% confidence intervals including the null value.

Because it was recognized that Study 337 was not powered for efficacy (due to feasibility in the setting of a rare disease) as well as the possibility that the adult condition (PPF) may have similarities to the pediatric condition (pediatric ILD), Bayesian analyses for FVC had been pre-specified to aid in the interpretation of efficacy. However, Bayesian analyses required a high degree of borrowing adult data in order for 95% (or even 80%) credible intervals to exclude the null value (e.g., ≥94% adult data borrowing for 95% credible intervals to exclude null value). This high level of borrowing would essentially require near full extrapolation of adult data to the pediatric population and is predicated on a high confidence in the similarity of diseases between adult and pediatric manifestations of the condition.

However, as noted in section 2.1, the overlap between adult and pediatric ILDs is unclear. Moreover, as noted in section 8.1.2 *Demographic and Baseline Characteristics*, the underlying ILDs enrolled in Study 337 differed markedly from those in the adult trial (INBUILD) [e.g., large proportion of surfactant protein deficiency patients]. As such, the extent of borrowing of adult data needed (≥92%) is not supported by the existing understanding of the pediatric and adult conditions as well as the observations of disparate ILDs enrolled between the adult and pediatric trials (1199.247 [INBUILD] and Study 337 [1199.337]).

In summary, based on the efficacy data discussed above, and considering the existing understanding of pediatric and adult ILDs, the data do not provide support for the efficacy of nintedanib (b) (4)

8.2. Review of Safety

8.2.1. Safety Review Approach

The focus in the safety portion of this review is on the randomized population that received at least one study drug dose (treated set) from Study 337. When relevant, discussion of subgroups is added, such as subgroup analyses based on age (ages 6-11 years old vs. 12 to 17 years old). Note that all safety analyses are for data up to DBL2 (all controlled safety data), which includes the blinded controlled treatment period for the patients enrolled after DBL1 (see Figure 7 showing Study Schematic).

The primary focus of this safety evaluation is the 24-week blinded treatment period (part A). Findings from the variable duration open-label portion (part B) are discussed when relevant.

8.2.2. Review of the Safety Database

Overall Exposure

Study 337 was the only clinical trial relevant to the target population (pediatric interstitial lung disease [ILD]).

Exposure during the 24-week blinded controlled treatment period is shown below in Table 13. In general, the median duration of exposure was comparable between the treatment arms. Dose reductions, treatment interruptions, and treatment discontinuations were more common in nintedanib-treated patients than placebo-treated patients. This is not surprising based on the known tolerability issues with nintedanib in adults.

Table 13: Exposure, 24 week Blinded Controlled Treatment Period, Safety population

Exposure, days	Placebo N=13	Nintedanib N=26
Mean (SD)	21 (6)	22 (6)
Median	24	24
Min, max	4, 24	3, 29
Exposure by thresholds, # of patients		
1 to 12 weeks	1 (8)	2 (8)
12 to 24 weeks	12 (92)	24 (92)
Treatment reduction, interruption, or discontinuation		
Patients with at least 1 dose reduction	1 (8)	4 (15)
Patients with at least 1 treatment interruption	1 (8)	11 (42)
Patients prematurely discontinuing treatment	0	3 (12)

Source: CSR 1199.337, Table 10:24 p.178

Adequacy of the safety database:

Given the rarity of pediatric ILD, this safety database is adequate for review. However, it is important to note that due to the small sample size of Study 337 and the absence of other relevant pediatric safety data for nintedanib, safety determinations are limited and safety concerns may persist.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no site investigations conducted by the Office of Scientific Investigation as there

were no issues regarding data integrity or submission quality.

Categorization of Adverse Events

MedDRA version 25.0 was used to code adverse events (AEs). AE and Serious AEs (SAEs) were defined per CFR 312.32.

Treatment emergent AEs were defined as AEs that occurred within 28 days (considered to be the residual effect period [REP] for nintedanib) from the last dose of study drug. Unless otherwise specified, safety analyses were based on TEAEs.

The SMC (safety monitoring committee) reviewed bone and dental imaging safety data at regular intervals. While AEs were recorded based on the local provider, information on SMC review was also available and is discussed in the review when pertinent. While there was an adjudication committee designated to review all deaths and major adverse cardiovascular events (MACE), neither occurred during the study.

Routine Clinical Tests

The measures used to assess the safety objectives were reasonable and included standard labs (hematology, chemistry, urinalysis), vital signs, bone and dental imaging, and height and weight measurements.

8.2.4. Safety Results

Safety Summary

Overall, in the 24-week double blind period, most patients had treatment emergent adverse events, balanced across treatment arms. However, more nintedanib-treated patients had severe AEs and AEs leading to permanent drug discontinuation. There were no deaths during the trial. These findings are shown in Table 14.

Table 14: Safety Summary, up to DBL2

	Nintedanib (N=26)	Placebo (N=13)
Patients with any TEAE	22 (85)	11 (85)
Patients with any severe TEAE	2 (8)	0
Patients with any TEAE leading to permanent drug discontinuation	2 (8)	0
Patients with any SAE	2 (8)	1 (8)
Patients with any fatal TEAE	0	0

Source: CSR Table 12:2; reviewer confirmed

Safety findings from the open label portion of Study 337 (part B) were generally similar for all the major safety categories (not shown).

Deaths
No deaths occurred during the conduct of Study 1199.337.

Serious Adverse Events

As shown in Table 14, there were 2 nintedanib patients and 1 placebo patient with SAEs during the blinded treatment period up to DBL2, described next. Of note, these 2 nintedanib patients with SAEs are identical to the two patients recorded as severe AEs (Table 14).

Patient (b) (6) was a 13-year-old white female with ILD associated with post-infectious obliterative bronchiolitis diagnosed 5 years prior to study enrollment (b) (6). After 172 days of nintedanib treatment, the patient was diagnosed with COVID-19 and was hospitalized. She had a headache, fever, cough, asthenia, ageusia, and dyspnea. She was discharged after approximately a week. The patient continued study drug through the hospitalization.

Patient (b) (6) was a 15-year-old Asian female with ILD related to toxic/radiation/drug induced pneumonitis, diagnosed 11 months prior to study drug initiation. After 155 days on study drug (with an interruption of ~6 weeks for logistical reasons), the patient developed tachycardia and hypoxia. She went to the local ER and was diagnosed with hypercapnia. She was hospitalized with an ILD exacerbation needing mechanical ventilation. SAEs of respiratory distress and increased carbon dioxide were recorded. Nintedanib was resumed during the hospitalization, and the patient was discharged after ~9 days. Of note, the onset of these SAEs occurred 43 days after temporarily stopping nintedanib.

The placebo-treated patient (patient (b) (6)) with an SAE was a 15-year-old female with a 3-year history of frontal lobe epilepsy and a prior history of SSc-ILD, who experienced worsening of frontal lobe epilepsy on Day 160 (~Week 23) after study drug initiation. Study drug was continued, and no other interventions made.

Overall, the SAEs noted above do not raise clear safety concerns for nintedanib in the pediatric population. However, given the small sample size and relatively short duration, it is difficult to make definitive conclusions.

Dropouts and/or Discontinuations Due to Adverse Effects

At the time of DBL2, there were no patients who had withdrawn from the study. However, there were 2 nintedanib-treated patients who had permanently discontinued study drug due to AEs (Table 7), described next.

Patient (b) (6) was an 8-year-old male with ILD from chronic hypersensitivity pneumonitis, diagnosed several months prior to enrollment. The patient had failure to thrive (low weight and height percentile values) and was on chronic glucocorticoid therapy with prednisone and methylprednisolone. After approximately 10 weeks of nintedanib therapy, a scheduled bone MRI was interpreted by local radiology review as having slight narrowing of the epiphyseal growth plate. This was reported by the investigator as the AE of "epiphyses premature fusion". However, central review showed no pathological findings and review by the SMC considered the slight narrowing as physiological. Central review of all bone MRIs at Weeks 12, 24, 36, 52, and 76 showed open epiphyses and no pathological findings other than small baseline Baker's cysts. This AE of "epiphyses premature fusion" led to study drug discontinuation after ~14 weeks of treatment.

Patient (b) (6) was a 6-year-old white female with ILD associated with surfactant protein deficiency, diagnosed 5 years prior to study enrollment. Prior to study drug initiation, the patient had had an elevated AST and ALT (56 [~1.5xULN], 92 U/L [~3x ULN], respectively), in which the etiology was unclear. After 84 days of nintedanib treatment, the patient had "liver injury" of mild intensity that led to permanent study drug discontinuation. The patient had had a fever, lymphadenopathy, and a mild elevation in ALT and AST > 3 X ULN, with normal bilirubin, eosinophils, and WBC. The study drug was permanently withdrawn within ~1week of these events. No therapy was given, and the enzyme levels normalized within 2 months. Of note, this patient had an elevation in liver enzymes 5x ULN ~1 month after permanent study drug discontinuation with accompanying eosinophilia/leukocytosis. This elevation resolved without intervention at a follow-up visit.

While review of the narratives above raises questions regarding relatedness to nintedanib, both of the above-described AEs (liver injury, epiphyses premature fusion) could be plausibly related to nintedanib and are not entirely unexpected as the adult safety profile for nintedanib includes warnings of "drug-induced liver injury" and nonclinical studies with nintedanib suggested bone and dental effects (in regions of active bone growth/turnover). It is also worth noting that AEs that led to permanent dose reductions or drug discontinuations in adults were primarily gastrointestinal (e.g., diarrhea), whereas the AEs that led to discontinuation in Study 337 were potentially more concerning (liver injury, adverse bone growth).

In summary, based on review of the narratives for AEs that led to permanent drug discontinuation, the relatedness to nintedanib is unclear. However, these AEs that led to permanent drug discontinuation do raise safety/tolerability concerns for the pediatric population as the events were identified in a small study with 6 months of exposure, and the events relate to either an identified risk for nintedanib in adults (hepatotoxicity) or an identified nonclinical toxicity (bone toxicity).

Treatment Emergent Adverse Event and Adverse Reactions

Most patients (85%) in Study 337 had TEAEs, generally balanced across treatment arms. The

most common TEAEs were in the Gastrointestinal disorders SOC and were diarrhea, dental caries, vomiting, abdominal pain, and nausea (all >10% incidence in each arm). This is shown in Table 15.

Table 15: Common TEAEs, > 1 patient in any arm, up to DBL2

SOC/PT	Nintedanib (N=26)	Placebo (N=13)
Patients with any TEAE	**22 (85)**	**11 (85)**
Gastrointestinal disorders	**22 (85)**	**11 (85)**
Diarrhea	10 (38)	2 (15)
Dental caries	7 (27)	3 (23)
Vomiting	7 (27)	3 (23)
Abdominal pain	5 (19)	3 (23)
Nausea	5 (19)	3 (23)
Tooth impacted	2 (8)	2 (15)
Feces soft	1 (4)	2 (15)
Infections and infestations	**10 (38)**	**3 (23)**
COVID-19	5 (19)	1 (8)
Rhinitis	3 (12)	0
General disorders and administration site conditions	**8 (31)**	**3 (23)**
Fatigue	2 (8)	2 (15)
Pyrexia	3 (12)	1 (8)
Respiratory, thoracic and mediastinal disorders	**4 (15)**	**4 (31)**
Oropharyngeal pain	1 (4)	2 (15)
Epistaxis	0	2 (15)
Nervous system disorders	**3 (12)**	**3 (23)**
Headache	3 (12)	1 (8)
Investigations	**2 (8)**	**3 (23)**
X-ray limb abnormal	0	2 (15)

Source: CSR Table 12:4; reviewer confirmed

Consistent with the known safety profile of nintedanib in adults, diarrhea was more common in nintedanib treated patients (38% vs 15%), albeit at a lower frequency than that noted in adult IPF or SSc-ILD patients. Based on the small sample size, it is not surprising that all risk difference confidence intervals for the above PTs included the null value (not shown), even for the AE of diarrhea with the largest risk difference of ~23%. Although the risk difference between treatment arms for dental caries was relatively small, it is worth noting that dental caries were more frequent in nintedanib-treated patients, as nonclinical dental toxicities were noted and these nonclinical dental adverse effects formed the basis for the lower age limit cutoff for Study 337 (i.e. age 6 years). Dental adverse effects are further discussed in Section 8.2.5.

Given the possibility of notable differences in safety between children (ages 6 to 11) and adolescents (12 to 17) based on physiological differences across the 6- to 17-year-old age range, subgroup safety analyses for all TEAEs were conducted for ages 6 to 11 years of age and 12 to 18 years of age. See Section 8.2.7.

Overall, the common TEAES were generally consistent with the known safety profile of nintedanib in adults in that gastrointestinal AEs were the most common adverse reactions, particularly diarrhea. Subgroup analyses by age did not raise clear safety concerns for a particular age-based subgroup, however, small sample sizes, particularly in the age-based subgroup analyses, limit the ability to rule out a definitive safety signal. In addition, dental caries was more common in nintedanib-treated patients, possibly related to dental concerns arising from nonclinical toxicology studies.

Laboratory Findings

Clinical laboratory tests included hematology, clinical chemistry and electrolytes, coagulation testing, and urinalyses. All laboratory analyses reflected results from a central laboratory rather than any local laboratories. Investigators used personal judgement in determining whether a laboratory finding was "clinically significant" (i.e., no pre-specified criteria). The vast majority of patients in both arms had normal laboratory values at baseline and during the trial. Shift table analyses and descriptive analyses from the Applicant were reviewed, and laboratory abnormalities verified by the review team. The following paragraph describes isolated cases that occurred within the blinded controlled treatment period.

For hematology, there was 1 nintedanib-treated patient with low erythrocytes, 1 nintedanib patient with low leukocytes, and 1 placebo patient with high eosinophils, all noted as "possibly clinically significant" by investigators. However, none of these findings resulted in intervention or study drug dosing changes. These observations are consistent with the absence of notable hematological AEs during Study 337. Similarly, for coagulation tests, there was 1 case of an elevated INR (INR=1.45) in a patient receiving nintedanib that did not require intervention or result in any bleeding or hematologic AE. For clinical chemistry, the vast majority of patients in both arms had normal electrolytes at baseline and during the trial with the exception of calcium levels: there were 6 nintedanib and 2 placebo-treated patients with elevated calcium values, none requiring intervention or deemed clinically significant. Given the known safety profile of nintedanib, whether GI symptoms such as nausea/constipation that occurred in several patients with elevated calcium levels is related to the electrolyte abnormality is unclear.

Liver function tests are discussed separately in section 8.2.5 *Hepatobiliary AEs*.

Overall, there were no new safety concerns raised in reviewing clinical laboratory findings.

Vital Signs

The Applicant performed analyses for vital signs of SBP, DBP, and pulse. Changes over the controlled period (24 weeks) were reviewed, as well as results out to 76 weeks (when data available). Review of these analyses did not reveal clinically significant changes (e.g., for placebo and nintedanib treated patients, respectively, mean change from baseline at 24 weeks was as follows: SBP -2.1mmHg and -3.9mmHg; DBP +1.7mmHg and -1.3mmHg; pulse -6.5bpm and -7.6bpm).

In addition, there were no AEs during the entire trial that would relate to abnormalities in these vital signs, with the exception of one nintedanib treated patient with the PT of "heart rate increased" (PT terms searched as part of review team analysis included: hypertension, hypotension, increased BP, decreased BP, heart rate decreased, bradycardia, tachycardia).

Body weight is discussed in detail in section 8.2.5.

Overall, these -findings do not raise new concerns in the pediatric population for use of nintedanib.

Electrocardiograms (ECGs)

There are no ECG or QT studies as part of this supplement. ECG sub studies and QT/QTc studies performed as part of nintedanib's IPF development program were reviewed by Dr. Miya Paterniti in her clinical review dated September 3, 2014.

Immunogenicity

Not applicable as nintedanib is a small molecule.

8.2.5. Analysis of Submission-Specific Safety Issues

Based on nintedanib's known safety profile in adults (current label) as well as nonclinical data relevant to the study population in Study 337, the following AEs of special interest (AESIs) were identified by the Applicant:

1. Gastrointestinal and Metabolic AEs
2. Bleeding and Hematological AEs
3. Hepatobiliary AEs
4. Bone and dental AEs

In addition, to these above AESIs, height and weight changes was also reviewed by the FDA review team.

Because some AEs that may be related to a particular medical issue can occur across system organ classes (SOCs) (e.g., dental disorders may include dental caries in Gastrointestinal disorders SOC, tooth abscess in Infections and infestations SOC, tooth facture in Injury, poisoning and procedural complications SOC, and supernumerary teeth in Congenital, familial and genetic disorders SOC), separate analyses were conducted based on groupings of AEs.

The Applicant grouped AEs/preferred terms and referred to groupings as "medical concepts". These "medical concept" groupings by the Applicant were reviewed by the FDA review team and felt to be reasonable (e.g., medical concept "dental disorders" included PTs of "dental caries", "tooth impacted", and other relevant AEs). In addition, FDA reviewer analyses using grouping of PT terms (selected by the FDA review team) were also conducted to verify the Applicant's medical concept-based analyses results. These grouping-based analyses are discussed when relevant.

Gastrointestinal and Metabolic AEs

While the overall incidence of gastrointestinal AEs was similar between arms, there were more nintedanib treated patients with diarrhea, dental caries, and vomiting, as shown in Table 16. However, risk difference confidence intervals included the null value for all PTs (not shown).

Table 16: Gastrointestinal disorders SOC AEs, >1 in any arm, nintedanib arm > placebo arm, up to DBL2

	Nintedanib (N=26)	Placebo (N=13)
Patients with any GI SOC AE	22 (85)	11 (85)
Diarrhea	10 (39)	2 (15)
Dental caries	7 (27)	3 (23)
Vomiting	7 (27)	3 (23)

Source: CSR Table 12:4, CSR Table 12:14; confirmed by reviewer analysis

The Applicant collected further information on diarrhea via a separate eCRF page. From that information collected, it was observed that diarrhea occurred most often in the first 2 weeks, did not lead to premature study drug discontinuation, was never severe, was mostly felt to be drug related, and always recovered (generally without treatment interruption).

With regard to other labeled warnings, there were no gastrointestinal perforations during the entire trial.

With regard to subgroup analysis by age, adolescents treated with nintedanib had more diarrhea, nausea, vomiting, and abdominal pain than children treated with nintedanib, whereas dental caries were more common in younger nintedanib patients (Table 13).

In the Metabolism and Nutrition Disorders SOC, there were no AEs with >1 patient in any arm. There was one nintedanib-treated patient with decreased appetite and dehydration and one placebo patient with increased appetite.

Overall, the GI and metabolic AEs observed in this small trial are consistent with the known safety profile of nintedanib in adults, and no new concerns are noted for the pediatric population studied.

Bleeding and Hematologic AEs

During the blinded controlled treatment period (up to DBL2), there were more placebo patients with bleeding or hematological AEs than nintedanib-treated patients (placebo 2[15%] vs. nintedanib 1[4%]). The nintedanib-treated patient (narrative in next paragraph) had a mild lower GI bleed and the placebo patients had epistaxis and rectal hemorrhage. No bleeding/hematological AE was serious.

Patient (b) (6) was a 10-year-old white Polish female with juvenile RA diagnosed with ILD who experienced a mild lower GI bleed after week 23 of nintedanib treatment. The presence of blood was noted once in the patient's stool after 3 days of constipation. There was no recurrence, additional symptoms, or interventions.

While nintedanib does carry a warning for arterial thromboembolic events, in Study 337 there were no cardiovascular or vascular thromboembolic adverse events reported.

Overall, there were no concerns raised for bleeding or hematological AEs related to nintedanib in Study 337.

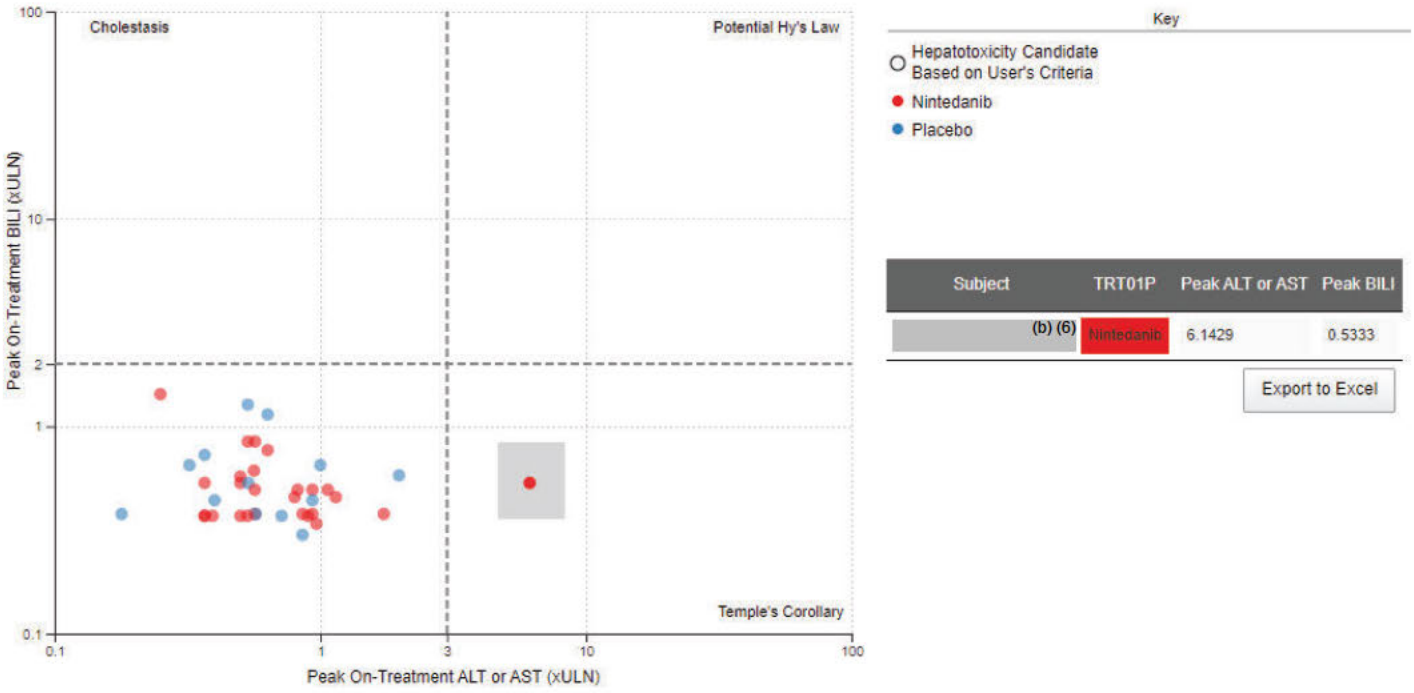
Hepatobiliary AEs

Liver enzyme elevations were assessed based on fold increase compared to upper limit of normal (ULN) e.g., > 3x ULN or > 5x ULN.

There were no patients during the trial that met Hy's law criteria.

There was one nintedanib-treated patient meeting Temple's corollary criteria, and one nintedanib-treated patient with an isolated elevated bilirubin level, but below 2x ULN. These are shown in Figure 10, and described next.

Figure 10: Hepatic Enzyme Analysis, Study 337, Treated Set, Blinded control period



Source: reviewer analysis, Analysis Studio

Patient (b) (6) had an ALT maximum >5x ULN that occurred 1 month after permanent study drug discontinuation. While elevations in liver enzymes earlier (> 3x ULN) led to study

drug discontinuation for this patient, there were no SAEs related to this event (see Section 8.2.4 *Dropouts and/or Discontinuations due to Adverse Effects* for narrative).

Patient (b) (6) had an isolated bilirubin elevation of 1.5x ULN which did not meet the Applicant's threshold for clinically significant (2 x ULN), was not associated with any changes in dosing (interruption, dose modification, or discontinuation), and was not reported as an AE.

With regard to other LFTs, there were no clinically relevant alkaline phosphatase elevations in nintedanib treated patients.

It is worth noting that one patient had an AE reported of elevated LFTs based on local laboratory values that are not in the central trial database, thus precluding inclusion in the hepatic safety exploration data shown in Figure 2. Patient (b) (6) was a 15-year-old female with multiple medical problems including ADHD, prosthetic right eye, iron deficiency, pectus excavatum, alpha thalassemia, bilateral retinoblastoma, and ILD diagnosed ~1 year prior to enrollment. After 70 days of nintedanib, the patient had a mild elevation in LFTs obtained in a local laboratory, reported (without quantitative data) as an AE. Based on the reporting severity of "mild" and the resolution of the AE without any dosing change or intervention, this is not felt to have been a safety concern.

During the open-label portion of the study, there were two patients with elevated liver enzymes:

1. Patient (b) (6) was a 16-year-old female with dermatomyositis and ILD diagnosed 3 years prior to enrollment. The patient was on prednisone therapy at baseline. After 358 days of nintedanib therapy, the patient had an AE reported of hepatic enzyme increased of moderate intensity. The patient had started mycophenolate mofetil (unknown start date) which was thought to play a role. This AE was not serious and did not lead to dosing modification or other intervention.
2. Patient (b) (6) had increased liver function tests that resulted in an SAE of liver injury. This patient was a 12-year-old Asian female with ILD diagnosed 5 years prior to enrollment. The patient was fed by a G-tube, had polyarthritis, and chronic steroid therapy. Throughout her study drug treatment course, she had had multiple episodes of nausea, vomiting, and diarrhea. After over one year of nintedanib treatment, the patient's dose was increased from 100mg to 150mg BID. After 22 days of the higher dose, the patient had an elevated ALT > 3x ULN and AST > 2.5x ULN, in association with nausea and vomiting. This was recorded as liver injury of moderate intensity. Study drug was interrupted due to this liver injury AE (no other interventions) and resumed after ~1.5months with the lower dose of 100mg.

Overall, the hepatobiliary safety findings in Study 337 are consistent with the known adult safety profile. However, whether a study with a longer controlled treatment period, and larger sample size would raise added concerns for hepatotoxicity in the pediatric population is unclear.

Bone, Dental, Height, and Weight related AEs

Bone adverse effects

Bone-related AEs were determined based on bone imaging of the epiphyseal plate near the femur/tibia.

There was one patient in each arm reported as having new growth plate disorders by Week 24 (up to DBL2; nintedanib 4% vs. placebo 8%), and two nintedanib treated patients with growth plate abnormalities identified on the day of starting treatment (not considered treatment related). Narratives for these 3 nintedanib-treated patients with bone abnormalities are described next.

Patient (b) (6) was a 12-year-old female with ILD diagnosed 10 years prior to enrollment. with a baseline history of osteopathy associated with long term glucocorticoid treatment. The patient had an abnormal bone MRI on the day of starting nintedanib treatment (recorded as AE "bone lesion") which showed mild intensity abnormal finding in the distal right femur/proximal tibia metaphyses (reported as T1/T2 hyposignal lesions). No action was taken related to this bone lesion and follow up scheduled bone MRIs at Weeks 12, 24, and 36 did not show worsening. Growth plates were open per central review for all MRIs. The bone MRI at Week 52 showed no abnormalities by central review, suggesting resolution. The investigator did not consider the adverse event of "bone lesion" to be related to study drug.

Patient (b) (6) was a 9-year-old male with ILD from toxic/radiation/drug induced causes, diagnosed 1 year prior to enrollment. The patient was receiving chronic glucocorticoid therapy. On the day of initiating nintedanib study drug treatment, a bone MRI showed potentially pathological metaphyseal lines at the proximal tibia. These findings remained unchanged for all follow up bone imaging for Weeks 12, 24, and 36. No action was taken as a result of the bone findings, nor any AE recorded.

Patient (b) (6) narrative is in section 8.2.4 *Dropouts and/or Discontinuations Due to Adverse Effects.* Briefly, bone imaging readings by central and local radiologists were discrepant (normal vs. abnormal, respectively) regarding epiphyseal closure/fusion. The investigator had reported the AE of "epiphyses premature fusion". Central review of all bone MRIs at Weeks 12, 24, 36, 52, and 76 showed open epiphyses and no pathological findings, suggesting the local review was erroneous. In addition, the patient had an increase in height of 4 cm over a 65-week follow-up period.

In considering the open-label safety data up to Week 52, 2 additional cases were noted of abnormal epiphyses (patients (b) (6)). Both were deemed by the SMC to be physiologic closures of the epiphyses in teenage females (ages 13 and 14 years), and not drug-related.

Based on balanced incidences across arms and narrative reviews, analyses of bone-imaging related AEs did not raise clear concerns for nintedanib use in this pediatric study population. As noted before, given the small sample size and short controlled treatment duration, lack of clear findings do not necessarily definitively rule out a safety concern in this population particularly in the context of the non-clinical findings.

Dental adverse effects

Dental adverse effects were determined by both dental examination (by dentists) as well as by dental imaging.

On dental examinations, there was a higher incidence of pathologic findings in nintedanib treated patients than placebo treated patients, up to week 24 (19% vs. 15%), increasing to 23% by Week 52 (uncontrolled open label data). Dental findings, recorded as AEs, included dental caries, malpositioned teeth, tooth impacted, tooth development disorder, tooth deposit, supernumerary teeth, tooth fracture, tooth abscess, dental cyst, dental plaque, and malocclusion. Other than "dental caries" and "tooth impacted", there were no AEs with >1 patient in any arm. Dental caries were more frequent in nintedanib-treated patients.

On dental imaging, there were 6 patients with stunted dental root growth, all in the nintedanib treatment arm. While this was reported during the open-label period, it was based on imaging done at the end of the double-blind period (Week 24) and centrally reviewed afterwards. In all 6 cases, treatment was interrupted at approximately the Week 24 timepoint, but resumed based on SMC pediatric dental evaluation. In the majority of cases, patients were on chronic oral corticosteroid treatment (patient (b) (6) was not). This information is summarized in Table 17.

Table 17: Patients with abnormal dental imaging, whole trial including OL portion, treated set

Patient ID	Age	Findings		SMC expert evaluation	Study Day
		24 weeks	52 weeks		
(b) (6)	14	Stunted growth of dental root	No stunted growth	No difference in radiographic presentation from baseline to Week 24 or 52. Impact of trial medication at age 14 unlikely	204
	12	Stunted growth of dental root	No stunted growth	Likely no difference from baseline to week 24 in the 3 teeth identified (15, 24, 47)	165

(b) (6)					
	16	Stunted growth of dental root	No stunted growth	No difference from baseline to week 24. Impact of trial medication at age 16 unlikely as root development typically completed by age 9/10	170
	6	Stunted growth of dental root	Stunted growth of dental root	Image quality insufficient week 24; high quality week 52 image shows normal development for 4 of 10 teeth	164
	15	Stunted growth of dental root	No stunted growth	Impact of trial medication at age 15 unlikely given root development teeth 24 and 25 typically complete by age 12	169
	13	Stunted growth of dental root	No stunted growth	Image positioning may account for appearance. Dental development progress appears normal	168

Source: CSR Table 12:19

Although the majority of stunted dental root growth was noted in adolescents and not in children (whom one may expect to be more affected based on known dental development patterns), this may not be that surprising based on the small sample size of the study as well as the 2:1 ratio of enrollment for adolescents. It may be difficult to uncover such a safety finding if it exists, and a larger and longer study may be needed. Also worth noting is that the interpretation of any dental or bone-related safety concern is confounded by the common chronic steroid usage in this population. This played a factor in many investigators' judgement of causality or relatedness determination.

Overall, dental imaging based adverse findings raise possible safety concerns for nintedanib, supported by nonclinical findings. While the SMC pediatric dental review did not raise concerns for the 6 nintedanib patients with stunted dental growth, the FDA review team remains concerned for possible dental safety issues, based on numerical differences seen in a small, relatively short duration study and known nonclinical concerns.

Body weight

Quantitative analyses were based on weight assessments conducted every several months over the entire trial. Qualitative analyses were based on adverse event reports of relevant AEs ("weight decreased" and "decreased appetite" were reported, and no other relevant AEs were reported).

With regard to quantitative data analyses, the mean change from baseline in body weight at Week 24 (up to DBL2) was -0.3 kg (SD 2.1kg) in the nintedanib group and +1.4 kg (SD 3.8kg) in the placebo group (*Source: CSR p.329)*. In light of the relatively short control period (24 weeks) and expected growth and weight gain in a pediatric population, these results are concerning based on the directional differences between arms (i.e., weight gain for placebo patients, weight loss for nintedanib patients). Moreover, individual patient quantitative data also raises concerns.

Two nintedanib treated patients lost >10% body weight over the course of the whole trial:

1. For patient (b) (6), "weight decreased" was reported as an AE approximately one year on nintedanib treatment (Day 364). The patient lost 5 kg from a 32 kg starting weight (16% weight loss).

2. For patient (b) (6), weight loss was not reported as an AE, however, "decreased appetite" was reported on Day 182 and the patient had lost 6 kg from a 47 kg starting weight (13% weight loss) at that time.

In light of patient (b) (6) not having a reported AE of "weight decreased" but having a "decreased appetite" AE reported, the FDA review team reviewed other cases of "decreased appetite" to determine if weight loss was also present in notable measure in those patients. There were two other patients with "decreased appetite" reported (patients (b) (6)), neither of whom had notable weight loss.

Similarly, patients with a reported AE of "weight decreased" were reviewed for quantitative weight change. Patient (b) (6) had "weight decreased" reported as an AE on Day 170 (Week 24) with weight measurements showing a drop from 43.1 kg to 39.7 kg (8% weight loss). Trial medication (nintedanib) was interrupted for ~40 days before restarting. In total, there were two patients in the open-label treatment period (part B) with AE of "weight decreased" reported, both of whom were in the nintedanib treatment arm for part A.

Given the small sample size, the weight related data from Study 337 is concerning based on the extent of weight loss in certain cases (>10%) as well as the summarized quantitative data for weight changes, particularly for the proposed pediatric target population with expected growth and development.

Height

Height was assessed via measurements of sitting height, standing height, and leg length at baseline and follow-up visits.

For standing height data up to DBL2, there was no difference between placebo and nintedanib treated patients at week 24 (adjusted mean changes from baseline in height at week 24: 1.3 cm each arm). Data from additional time points (weeks 12, 36, 52, 64) were reviewed and were similar (95% confidence intervals all included the null, became wider at later timepoints due to less evaluable data, and all adjusted mean differences between nintedanib and placebo arms were small (<0.5cm) and with changing directionality (e.g., negative to positive, suggestive of no consistent trend).

Sitting height measurement were measured incorrectly in a large proportion of patients (10 nintedanib patients, 6 placebo patients). As such, the existing reliable dataset was too small to provide interpretable data.

Leg length measurements up to DBL2 at week 24 did not show notable differences between arms. Specifically, adjusted mean changes from baseline in leg length for the left leg were 1.7 cm [0.8, 2.7] nintedanib vs. 1.6 cm [0.3, 2.9] placebo, and for the right leg were 1.6 cm [0.6,2.6] nintedanib vs. 1.6 cm [0.3,2.9] placebo.

Of note, Z-scores were used to account for effects of age and gender on growth. Analyses of z-score adjustments (e.g., height-for-age-z-score slope) did not raise new concerns.

Overall, measurements of standing height and sitting height did not raise clear concerns, however, the small sample size and short controlled duration period preclude the ability to definitely rule out growth concerns related to nintedanib use in the pediatric population. Because a large proportion of leg length measurements were inaccurate, no conclusions can be drawn from these assessments.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable

8.2.7. Safety Analyses by Demographic Subgroups

Given the possibility of notable differences in safety between children (ages 6 to 11) and adolescents (12 to 17) based on rapidly changing physiology across the 6- to 17-year-old age range, subgroup safety analyses for all TEAEs were conducted for ages 6 to 11 years of age and 12 to 18 years of age. This is shown in Table 18.

Table 18: Age-based Subgroup Analyses All TEAEs, up to DBL2, >1 patient in any arm

	Adolescents (12-17 years)		Children (6 -11 years)	
	Nintedanib (N=18) n(%)	Placebo (N=9) n(%)	Nintedanib (N=8) n(%)	Placebo (N=4) n(%)
Patients with any TEAE	16 (89)	7 (78)	6 (75)	4 (100)
SOC/PT				
Gastrointestinal disorders	16 (89)	7 (78)	6 (75)	4 (100)
Diarrhea	8 (44)	2 (22)	2 (25)	0
Dental caries	4 (22)	2 (22)	3 (38)	1 (25)
Vomiting	5 (28)	1 (11)	2 (25)	2 (50)
Abdominal pain	4 (22)	1 (11)	1 (12)	2 (50)

Nausea	5 (28)	1 (11)	0	2 (50)
Tooth impacted	2 (11)	2 (22)	0	0
Constipation	0	1 (11)	2 (25)	0
Feces soft	1 (6)	0	0	2 (50)
Infections and infestations	6 (33)	2 (22)	4 (50)	1 (25)
COVID-19	3 (17)	0	2 (25)	1 (25)
Rhinitis	1 (6)	0	2 (25)	0
General disorders and administration site conditions	5 (28)	3 (33)	3 (38)	0
Fatigue	2 (11)	2 (22)	0	0
Pyrexia	1 (6)	1 (11)	2 (25)	0
Chest pain	2 (11)	0	0	0
Respiratory, thoracic and mediastinal disorders	3 (17)	2 (22)	1 (12)	2 (50)
Oropharyngeal pain	1 (6)	2 (22)	0	0
Epistaxis	0	0	0	2 (50)
Nervous system disorders	3 (17)	3 (33)	0	0
Headache	3 (17)	1 (11)	0	0

Source: FDA review team (Analysis Studio, ADSL, ADAE)

Subgroup analyses based on ages 6-11 and 12-17 years suggested more diarrhea and nausea (>~15% difference between groups) in adolescents treated with nintedanib than children treated with nintedanib. When incidences are considered in the context of the placebo comparators, nausea and vomiting are more common in the adolescents (than children) taking nintedanib. It is worth noting that children treated with nintedanib had a higher incidence of dental caries, as one may expect that dental adverse effects may be more likely to be observed in the younger subpopulation based on nonclinical findings. However, given the small sample sizes, conclusions cannot be drawn.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The current nintedanib label notes the following adverse reactions identified in the post-approval (postmarketing) period: drug-induced liver injury, non-serious and serious bleeding events, some of which were fatal, pancreatitis, thrombocytopenia, rash, pruritus. Several of these AEs or related-AEs are discussed in section 8.2.5 of this review.

Expectations on Safety in the Postmarket Setting

Not applicable (b) (4)

8.2.10. Integrated Assessment of Safety

The safety data submitted by the Applicant for analysis with this sNDA was sufficient for review. The data is derived from Study 337 which was a 2-part trial (part A fixed 24 weeks randomized, double-blinded, placebo-controlled treatment period, part B variable duration, open-label, single arm). Given the rarity of the disease, the total safety database from this study, while small, was reasonable for review. In addition, the safety assessments, which included an evaluation of deaths, SAEs, TEAEs, AEs leading to drug discontinuation, laboratory findings, bone imaging, dental exam and imaging, height measurements, weight measurement, and vital signs, were reasonable.

In the context of a small sample size (N=39) and relatively short, controlled treatment duration (24 weeks), there were safety concerns noted. While there were no deaths during the study and SAEs were balanced and infrequent, there were concerns related to AEs leading to treatment discontinuation, as well as AESIs. AEs leading to treatment discontinuation were more frequent in nintedanib patients and different than those seen in the adult indications. Specifically, the types of AEs that led to discontinuation in Study 337 (hepatotoxicity, bone toxicity) were different than those AEs that led to drug discontinuation in the adult indications (e.g., diarrhea). With regard to AESIs, dental imaging related AEs were more commonly seen in nintedanib treated patients, which is plausibly supported by nonclinical data. Furthermore, quantitative and qualitative data for weight loss also raised concern for nintedanib use in this population. As for common AEs, nintedanib treated patients had more GI AEs, consistent with the adult profile.

Analyses of subgroups (e.g., by age) did not raise clear concerns, albeit markedly limited by small sample sizes in a study that already had a limited sample size.

In conclusion, while the small sample size and short controlled treatment duration limit the

ability to make definitive safety conclusions, there are concerns raised for weight loss and dental adverse effects, both of which are plausible and supported by the adult safety profile for nintedanib as well as the nonclinical data. These are of particular concern given that they were identified in a small, relatively short duration study. Whether a longer and larger study would uncover new safety concerns is unclear.

8.3. Statistical Issues

The statistical issue that will be discussed in more detail is the supportive efficacy analysis of the change from baseline in FVC% predicted at Week 24 by use of a Bayesian approach with a prior derived from adult data.

In Study 337, the adjusted mean observed treatment effect for the change from baseline in FVC% predicted at Week 24 was 1.21 (95% CI -3.40, 5.81) which was lower than the one from the adult component (1.69) of the robust MAP prior. By the data-prior conflict, the weight on the informative element would have decreased by the feature of robust mixture prior approach called 'dynamic borrowing'. Since this updated weight is used to form the posterior distribution that is used for performing inferences in the pediatric subjects, we suspect that it could have reduced the probability of correctly inferring efficacy (e.g. power) in Study 337. As observed in the operating characteristics provided in the SAP (Table 19), the probability of correctly inferring efficacy for base case scenario (a mean observed treatment effect of Δ=1.65) for the pre-specified weight (56%) was 77% for one-sided 90% evidence level. Therefore, the probability of correctly inferring efficacy with the actual data in Study 337 could have been less than what was observed (77%) under the base case scenario, causing the Bayesian analysis result less statistically reliable. We also note that, for more stringent evidence level (one-sided 97.5%), the probability of correctly inferring efficacy in this study would be less than 36% for Study 337.

Table 19: Operating Characteristics

Scenario	Prior weight on adult data (%)	Probabilities of correctly (base case, S1, S2, S5, S6) or falsely (S3, S4) inferring efficacy for different one-sided evidence levels (%)			
		97.5%	95%	90%	80%
Base case	0	11	18	27	43
	10	13	22	37	56
	20	17	28	46	68
	30	20	36	56	76
	40	25	43	65	82
	50	32	52	72	87
	56	36	57	77	90
	60	39	61	79	91
	70	48	70	85	94
	80	59	79	91	96
	90	73	88	95	98
	100	92	98	100	100

Base case scenario (an effect size of 1.65 and standard error of 2.49).

Source: SAP Table 9.6.5: 1, p.90

In addition, the Applicant calculated the realized amount of borrowing from the adult component of the prior (ESS_{prior}). The calculation method used for effective sample size was the expected local information-ratio (ELIR). Based on this approach, the degree of borrowing needed to meet the decision rule (that the 80% credible interval from the posterior distribution excludes 0 for the chosen weight of 56%) was 370 which corresponds to borrowing approximately 90% of adult data relative to the collected pediatric data (370 ÷ (370+39+1) where the '1' is the unit information from the noninformative element). However, we note that this approach is usually data-independent (information from the target population is not incorporated). Furthermore, the degree of borrowing heavily depends on the effective sample size calculation methods used. For example, effective sample size for the weight of 50% according to the Morita method was 1060 (Table 20).

Table 20: Effective Sample Size (ESS) Calculation

Weight of informative component of robust MAP prior	Effective sample size	
	ELIR method	Morita method
0.1	40	841
0.2	102	965
0.3	173	1016
0.4	247	1043
0.5	323	1060
0.6	402	1072
0.7	482	1080
0.8	564	1087
0.9	647	1092

Source: Response to FDA Comments (dated Oct 12, 2021) Table 5, p.9

The Applicant also calculated the total effective sample size contributing to the posterior distribution of the target population ($ESS_{posterior}$). This sample size could be leveraged to derive the 'current' effective sample size of the informative element ($ECSS_{inform}$) after it is updated with data from the target population. The Applicant noted that prior and posterior effective sample size may vary considerably and implausibly (i.e. predictively inconsistently), e.g., when the ELIR method is applied to the proposed robust mixture prior, as shown in Table 21 (see ESS_{prior} vs. $ECSS_{inform}$). For example, for the base case scenario (an effect size of 1.65 and standard error of 2.49) at the weight of 0.5, the effective sample size of prior is 323 whereas $ECSS_{inform}$ is 528.

Table 21: Prior vs. Posterior Effective Sample Size (ESS)

Weight of informative component of robust MAP prior	**Effective sample size (ELIR method)**		**$ECSS_{inform}$**
	ESS_{prior}	**$ESS_{posterior}$[1]**	**$ESS_{posterior}$ - 39 - 1**
0.1	40	158	118
0.2	102	310	270
0.3	173	421	381
0.4	247	504	464
0.5	323	568	528

0.6	402	619	579
0.7	482	661	621
0.8	564	696	656
0.9	647	726	686

[1] Calculated for base case scenario (an effect size of 1.65 and standard error of 2.49).

Source: Modified from Response to FDA Comments (dated Oct 12, 2021) Part D: Effective sample size, p.8

After observing the adjusted mean treatment effect for the change from baseline in FVC% predicted at Week 24 of 1.21 (with a standard error of 2.25) for the pediatric subjects in Study 337, the reviewer calculated $ECSS_{inform}$ of 627 (based on $ESS_{posterior}$ = 667) at the pre-specified weight of 0.56, which corresponds to borrowing approximately 94% of adult data relative to the collected pediatric data.

The difference in ESS calculations suggests that, although we acknowledge demonstration of efficacy in pediatric subjects would require inclusion of large amounts of data from adults for this study, it remains challenging to identify a reliable measure of amount of borrowing occurred in the Bayesian borrowing analysis. We also note that, the sample size was capped for Study 337, therefore, the large amount of borrowing was expected in the study.

8.4. Conclusions and Recommendations

(b) (4)

.

The Applicant completed Study 1199.337 (Study 337), a randomized, placebo-controlled, 2-part (part A: fixed 24-week treatment period, part B: variable duration) safety/PK study in patients ages 6 to 17 years old with ILD. The patients enrolled had ILDs due to various etiologies (e.g., surfactant protein deficiency, systemic sclerosis) and were all either severe and/or progressive (based on worsening imaging, radiography, and/or symptoms). The primary endpoint was safety/PK, and secondary endpoints included various efficacy measures (e.g., FVC, 6MW, SpO2). Given feasibility issues with patient enrollment due to the rarity of the disease, this trial was not designed with efficacy as the primary objective. However, to aid in the interpretation of the efficacy, in addition to frequentist statistical analyses, Bayesian efficacy analyses were performed using pre-specified methods which borrowed adult data from nintedanib trials in adults ILDs.

With regard to efficacy, results from both the FVC and non-FVC related endpoints did not provide support for efficacy based on frequentist analyses. Point estimates for results from traditional (frequentist) statistical analyses for change-in-FVC endpoints were modest (1.2% treatment difference) and 95% confidence intervals included the null value. Results from pre-specified Bayesian analyses were such that a high degree of borrowing from adult data was

needed (90%) in order to achieve results where the 80% credible interval excluded the null for the pre-specified Bayesian weight (0.56). Moreover, in order to achieve 95% credible intervals that excluded the null (which is more typically used in Bayesian analyses) borrowing of 94% from adult data was necessary. Such a high degree of borrowing would equate to near full extrapolation of pediatric treatment effect from adult data. Close to full extrapolation does not appear to be scientifically justified given the notable differences in the adult and pediatric conditions (see section 2.1), and the differences observed in the underlying causes of ILD in pediatric patients enrolled in Study 337 compared to the underlying causes observed from the adult ILD trials from which data were borrowed. Overall, based on these data, there remains considerable uncertainty regarding the benefit of nintedanib in this pediatric population; (b) (4)

(b) (4) trial results also raised safety concerns related to weight loss and dental adverse effects, both of which were plausible based on either adult data (USPI label section 6, weight loss) or nonclinical studies (dentopathy in mouse studies). These safety concerns are noteworthy as they were observed in a small trial of relatively short duration and are relevant to the pediatric population given their expected growth and development.

(b) (4) the benefit-risk assessment is not favorable for nintedanib for the treatment of fibrosing interstitial ILD in patients 6 to 17 years of age.

In conclusion, (b) (4) Study 337 has fulfilled PREA PMR 3807-1 and has addressed the WR issued on 10/27/2020. In order to provide clinicians with the pediatric data generated from Study 337, (b) (4) the Division will also request that the Applicant submit a labeling supplement to amend Section 8.4 of the USPI to include results from Study 337.

9 Advisory Committee Meeting and Other External Consultations

No Advisory committee meeting is planned for this product. No other external consultations are planned for this product.

10 Pediatrics

This review is focused on a pediatric indication.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

(b) (4) However, relevant information on pediatric investigations (i.e., Study 337) will be added to the product label under section 8.4 *Pediatric Use* to inform pediatricians of the available data. As such, a request will be sent to the Applicant to submit a separate labelling supplement for purposes of revising section 8.4 as follows:

> *The safety and effectiveness of OFEV have not been established in pediatric patients for the treatment of fibrosing interstitial lung diseases. Effectiveness was not demonstrated in a randomized, double-blind, placebo-controlled study conducted in 26 OFEV-treated pediatric patients aged 6 to 17 years for fibrosing interstitial lung diseases, who were treated with OFEV based on weight.*
>
> *Animal Toxicity Data*
> *In repeat-dose toxicology studies, young animals (mice, rats, and monkeys) dosed with nintedanib showed irreversible changes in the bone and teeth. Bone changes include thickening of the growth plate in all species and hypertrophic chondrocytes in mice. Tooth changes include broken incisors and discoloration in rodents. These changes were irreversible after discontinuation of nintedanib treatment.*

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS are needed for this application.

13 Postmarketing Requirements and Commitment

Not applicable.

14 Deputy Division Director (DPACC) Comments

Boehringer Ingelheim (BI), has submitted supplemental NDA (sNDA 205832-023) for nintedanib (b) (4) Nintedanib is a small molecule receptor and non-receptor tyrosine kinase inhibitor. It is approved for the treatment of idiopathic pulmonary fibrosis (IPF), systemic sclerosis interstitial lung disease (SSc-ILD), and chronic fibrosing ILDs with a progressive phenotype (also referred to as progressive pulmonary fibrosis [PPF]), at a dosage regimen of 150 mg oral twice daily. As part of a PREA post-marketing requirement (PMR 3807-1) after approval for the PPF indication, the Applicant conducted Study 1199.337 (Study 337). Study 337 is also the subject of a Written Request issued on October 27, 2020. In this supplemental NDA, the Applicant has submitted the results of Study 337 to address PMR 3807-1, the Written Request, (b) (4)

Study 337 was a randomized, placebo-controlled, 2-part (part A: fixed 24-week treatment period, part B: variable duration) safety/PK study in patients ages 6 to 17 years old with ILD. The patients enrolled had ILDs due to various etiologies (e.g., surfactant protein deficiency, systemic sclerosis) and were all either severe and/or progressive (based on worsening imaging, radiography, and/or symptoms). The primary endpoint was safety/PK, and secondary endpoints included various efficacy measures (e.g., FVC, 6MW, SpO2). Given feasibility issues with patient enrollment due to the rarity of the disease, this trial was not designed with efficacy as the primary objective. However, to aid in the interpretation of the efficacy, in addition to frequentist statistical analyses, Bayesian efficacy analyses were performed using pre-specified methods which borrowed adult data from nintedanib trials in adults ILDs.

Using frequentist statistical analysis, the treatment effect measured by change in FVC-based endpoints was modest (1.2% treatment difference in ppFVC), and not statistically significant. As pre-specified, Bayesian analyses were used, borrowing from adult data. During the review of

this supplement, it became apparent that the pre-specified Bayesian weight (0.56) equated to borrowing of 90-94% of data from adults, depending on whether the 80% or 90% credible intervals were used. Based on the current understanding of fibrosing ILDs in children and adults, and the differences in etiology and natural history, this degree of borrowing – which equates to nearly full extrapolation – is not scientifically justified. (b) (4) . In addition, several safety concerns relevant to a growing/developing pediatric population were identified (weight loss, dental adverse events). (b) (4) (b) (4)

(b) (4)

Study 337 did satisfy both PMR 3807-1 and the associated Written Request. (b) (6) the Division will request a labeling supplement to update Section 8.4 of the USPI to include the result of Study 337.

15 Appendices

15.1. References

1. Nonclinical original NDA review completed by Dr. Luqi Pei on August 28, 2014 (DARRTS ID# 3618575),
2. Nonclinical labeling review completed by Dr. Luqi Pei on September 15, 2023 (DARRTS ID# 5244859)
3. Dallow N, Best N, Montague TH. Better decision making in drug development through adoption of formal prior elicitation. Pharm Stat. 2018 Jul;17(4):301-316.
4. Gosling JP. SHELF: The Sheffield Elicitation Framework. In: Dias L C, Morton A, Quigley J (eds.). Elicitation: The science and art of structuring judgement. Springer International Publishing, 2018.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 1199.337

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 335		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☒	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology Appendices

Nintedanib affects bone growth and development in young animals. Table 22 lists oral toxicity studies of the drug with longest treatment duration in animals. The treatment duration was 3, 6, and 12 months in mice, rats, and monkeys, respectively. These animals were generally young when the dosing started. Nintedanib affected the bone structures in every species and the teeth in rodents. Bone changes include thickening of the growth plate in all species and hypertrophic chondrocytes in mice. Tooth changes include broken incisors and discoloration in rodents. These changes were irreversible after discontinuation of nintedanib treatment. The NOAEL was 5 mg/kg/day in rats, and unestablished in mice and monkeys.

Table 22: Toxicity Studies Evaluating the Effects of Nintedanib on the Bones and Tooth Development in Young Animals

	Mouse	**Rat**	**Monkey**
Study Reference No.	**U10-1798**	**U05-1843**	**U10-1875**
Treatment duration (week)	13	26	52
Nintedanib (mg/kg/day)	10, 30, 100	5, 20, 80	10, 20, 60/45/30 [a]
AUC (ng.h/mL) in LD group [b]	233 - 242	16.4 – 29.2	506 - 786
Age of animals (Weeks) [c]	5 – 6	8 - 9	123 – 143
Bone finding			
Growth plate	Thickening growth plate at ≥ LD	Thickening of epiphyseal cartilage at ≥ MD	Thickening of growth plate at ≥ LD
Articular cartilage	Chondrocyte swelling	-	-
Dental finding	Dentopathy at HD [d]	Dentopathy at ≥ MD	-
NOAEL (mg/kg/day)	Not established	5	Not established
Reversible?	Unknown	No [e]	No [e]
Ref. review (DARRTS #)	2841259	2944664	2944664

Source: Nonclinical labeling review completed by Dr. Luqi Pei on September 15, 2023 (DARRTS ID# 5244859)

LD - low dose, MD = mid dose, HD = high dose, and NOAEL = No Observed Adverse Effect Level.

a. Nintedanib doses in the high dose group were 60, 0, 45, and 30 mg/kg/day during weeks 1-3, 4-6, 7-26, and 26-55, respectively.

b. AUC value of the low dose group at the end of the treatment period.

c. Animal age when dosing started.
d. Dentopathy includes at least one of the following observations: fracture, pulp cavity exposed, atrophy of odontoblasts, and formation of dysplastic dentine.
e. The recovery period was 4 weeks in duration.

The review considers the effect of nintedanib on bone and tooth development relevant to humans because tyrosine kinase inhibitors (TKI) are known to affect bone metabolism (Endocrine-Related Cancer, 2014;21(3):R247-59). See the nonclinical NDA review and the nonclinical labeling review completed by Dr. Luqi Pei on August 28, 2014, and September 15, 2023 (DARRTS ID# 3618575 and 5244859, respectively) under NDA 208532 for details.

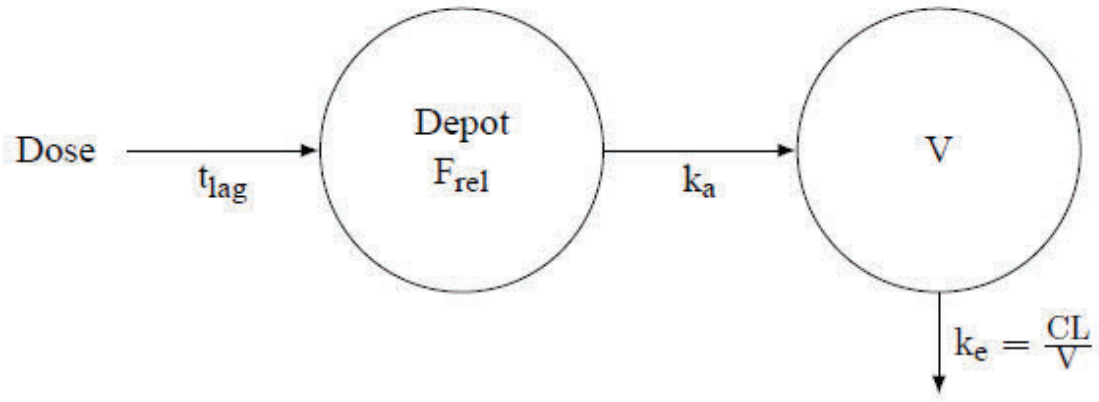
15.4. OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1. Population Pharmacokinetic Analysis

The Applicant conducted a PopPK analysis to evaluate nintedanib PK in pediatric patients. The PK external-evaluation and base models were based on a model that was previously developed on nintedanib PK data in adult patients with IPF, SSc-ILD and PF-ILD.

The previously developed nintedanib PopPK model in adult patients with IPF, SSc-ILD and PF-ILD was a one-compartment model with a lag-time followed by first-order absorption and a first-order elimination from the central compartment. IIV terms were included on apparent volume of distribution (V/F), first-order absorption rate constant (ka) and relative bioavailability (Frel), and interoccasion variability (IOV) was included on Frel. Covariate effects of baseline body weight (using allometric scaling with scaling centered around 75 kg and fixed exponents of 1 on V/F and 0.75 on apparent clearance (CL/F)) and ethnicity, SSc-ILD and lactate dehydrogenase (LDH) level at baseline on Frel were included. The structure of the base population PK model for nintedanib is depicted in Figure 11.

Figure 11 Illustration of the base population PK model for nintedanib



Source: Figure 28 in Pop PK and pop PKPD for nintedanib in pediatric patients with fibrosing interstitial lung disease (c37084509-03)

Fixed and random effects (population) parameters for the pre-specified model were estimated using the PRIOR functionality in NONMEM, using the NWPRI functionality. The prior point estimates and covariance matrix in NONMEM (from fitting the pre-specified model to the legacy data) were used to generate the NONMEM prior.

The population PK model parameter estimates of the base nintedanib model are presented in Table 23, in comparison to the external evaluation model. All model parameters, except RUV, were supported by the adult prior.

Table 23: Parameter estimates of the base nintedanib population PK model, in comparison to the external evaluation model.

		Base model			External evaluation model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
CL/F[a]*	(L/h)	909	2.31		909		
V/F[b]*	(L)	1.06E+04	4.33		1.10E+04		
k_a*	(/h)	2.72	11.6		2.85		
t_{lag}*	(h)	0.715	3.41		0.675		
Other ethnicities[c] on F_{rel}*	Fraction change	0.331	13.2		0.327		
Korean on F_{rel}*	Fraction change	-0.143	37.1		-0.152		
SSc-ILD on F_{rel}*	Fraction change	-0.145	26.3		-0.164		
LDH on F_{rel}*		0.00150	18.1		0.00155		
IIV V*	(CV)	0.312	10.4	21.4	0.289		32.9
IIV k_a*	(CV)	1.25	8.78	24.6	1.25		32.9
IIV F_{rel}*	(CV)	0.419	4.02	3.29	0.413		1.81
IOV F_{rel}*	(CV)	0.314	4.54	11.3	0.307		13.7
RUV	(CV)	0.390	4.42	12.2	0.445		16.4

[a]Adjusted to body weight: $TVP_i = P_{population} \cdot \left(\frac{WT_i}{75}\right)^{0.75}$
[b]Adjusted to body weight: $TVP_i = P_{population} \cdot \frac{WT_i}{75}$
[c]Chinese/Taiwanese/Indian/Japanese/Other Asian/Black/American Indian/Alaska Native.
* For the base model, supported by adult priors
Source: Table 10 in Pop PK and pop PKPD for nintedanib in pediatric patients with fibrosing interstitial lung disease (c37084509-03)

The parameter estimates of the final nintedanib population PK model are presented in Table 24, in comparison to the base model.

Table 24: Parameter estimates of the final nintedanib population PK model, in comparison to the base nintedanib population PK model.

		Final model			Base model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
CL/F[a]*	(L/h)	910	2.31		909	2.31	
V/F[b]*	(L)	1.08E+04	4.25		1.06E+04	4.33	
k_a*	(/h)	2.75	11.5		2.72	11.6	
t_{lag}*	(h)	0.713	3.25		0.715	3.41	
Other ethnicities[c] on F_{rel}*	Fraction change	0.331	13.3		0.331	13.2	
Korean on F_{rel}*	Fraction change	-0.147	36.2		-0.143	37.1	
SSc-ILD on F_{rel}*	Fraction change	-0.146	26.2		-0.145	26.3	
LDH on F_{rel}*		0.00154	17.7		0.00150	18.1	
Ped. autoimmune ILD on V	Fraction change	-0.282	33.0				
Pediatric age on IOV F_{rel}	change per yoa	-0.0539	54.7				
IIV V*	(CV)	0.303	10.0	24.2	0.312	10.4	21.4
IIV k_a*	(CV)	1.26	8.77	22.3	1.25	8.78	24.6
IIV F_{rel}*	(CV)	0.415	4.05	15.5	0.419	4.02	3.29
IOV F_{rel}*	(CV)	0.308	4.58	17.7	0.314	4.54	11.3
RUV	(CV)	0.384	4.32	12.3	0.390	4.42	12.2

[a]Adjusted to body weight: $TVP_i = P_{population} \cdot \left(\frac{WT_i}{75}\right)^{0.75}$

[b]Adjusted to body weight: $TVP_i = P_{population} \cdot \frac{WT_i}{75}$

[c]Chinese/Taiwanese/Indian/Japanese/Other Asian/Black/American Indian/Alaska Native.

* Supported by adult priors

Source: Table 12 in Pop PK and pop PKPD for nintedanib in pediatric patients with fibrosing interstitial lung disease (c37084509-03)

15.4.2. Exposure Response Analysis

The PKPD external-evaluation and starting models for %predicted FVC and FVC Z-score consisted of a linear placebo model and an maximum effect (Emax) model to describe the relationship between nintedanib Ctrough,ss and response, for both endpoints, respectively.

The base model consisted of a linear placebo model and an Emax model to describe the relationship between nintedanib Ctrough,ss and %predicted FVC response.

The population PKPD model parameter estimates of the base %predicted FVC model are presented in Table 25 in comparison to the external evaluation model.

Table 25: Parameter estimates of the base %predicted FVC PKPD model, in comparison to the %predicted FVC external evaluation model

		Base model			External evaluation model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
Baseline	%	55.0	6.74		71.0		
Slope*	%/year	-4.74	4.25		-4.78		
E_{max}*	%/year	4.31	11.6		4.34		
EC_{50}*	nM	7.97	27.7		8.24		
IIV Baseline	CV	0.420	11.4	0	0.221		0
IIV Slope*	SD, %/year	5.60	2.17	11.5	5.58		4.51
IIV RUV	CV	0.281	23.6	14.4	0.395		13.9
Prop. RUV	CV	0.0244	39.3	5.38	0.0183		0
Add. RUV	%	2.68	14.1	5.38	2.13		0

OFV of Base model and External evaluation model cannot be compared: the OFV of the Base model includes the prior information and the OFV of the External evaluation model is based only on analysis data.
* For the base model, supported by adult priors

Source: Table 15 in Pop PK and pop PKPD for nintedanib in pediatric patients with fibrosing interstitial lung disease (c37084509-03)

The final model for %predicted FVC consisted of a linear placebo model, with a covariate effect describing the change in pediatric annual rate of decline, and an Emax model to describe the relationship between nintedanib Ctrough,ss and %predicted FVC response.

The parameter estimates of the final %predicted FVC model are presented in Table 26, in comparison to the base model.

Table 26: Parameter estimates of the final %predicted FVC model, in comparison to the base %predicted FVC model

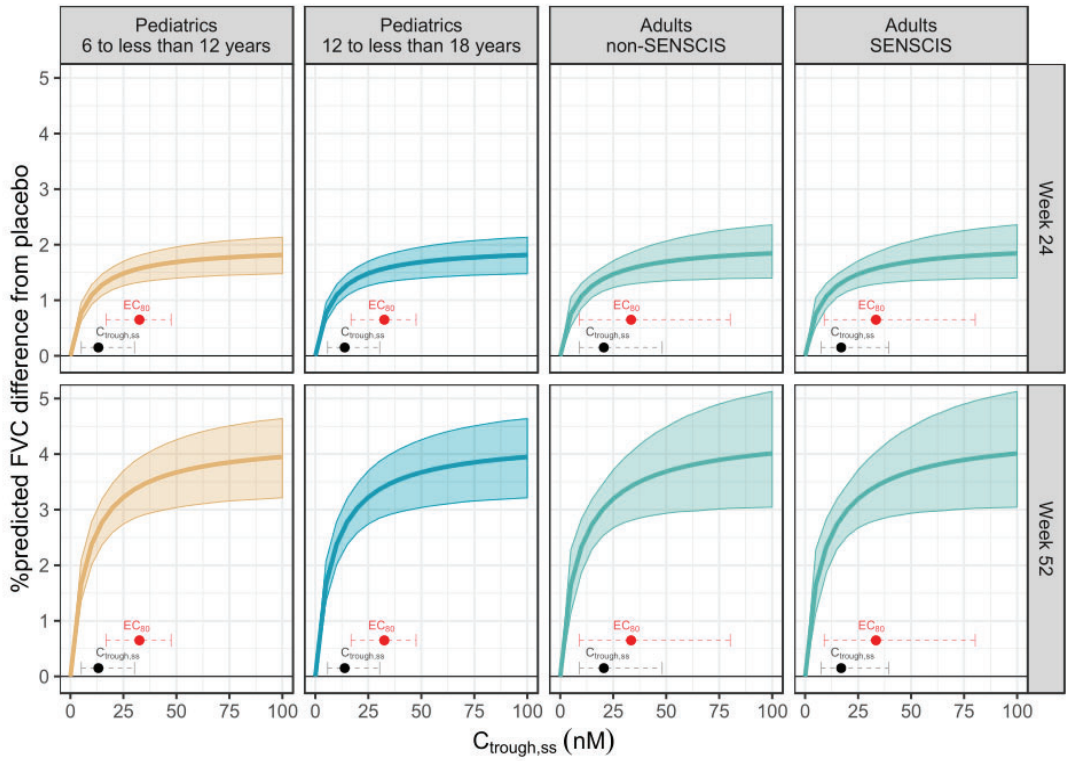
		Final model			Base model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
Baseline	%	54.7	6.78		55.0	6.74	
Slope*	%/year	-4.77	4.22		-4.74	4.25	
E_{max}*	%/year	4.27	12.3		4.31	11.6	
EC_{50}*	nM	8.13	28.6		7.97	27.7	
Pediatric change in Slope[a]	%/year	2.96	37.9				
IIV Baseline	CV	0.422	11.4	0	0.420	11.4	0
IIV Slope*	SD, %/year	5.58	2.17	14.1	5.60	2.17	11.5
IIV RUV	CV	0.295	22.9	12.8	0.281	23.6	14.4
Prop. RUV	CV	0.0242	40.0	5.11	0.0244	39.3	5.38
Add. RUV	%	2.66	14.4	5.11	2.68	14.1	5.38

* supported by adult priors.
[a] Translating into a Slope of -1.81 %predicted FVC/year for a pediatric patient.

Source: Table 17 in Pop PK and pop PKPD for nintedanib in pediatric patients with fibrosing interstitial lung disease (c37084509-03)

The model estimated ER relationship of FVCpp is depicted in Figure 12.

Figure 12: Typical population predictions of %predicted FVC difference from placebo versus $C_{trough,ss}$ for the final %predicted FVC model, stratified by age group and by study for adults.



Source: Figure 48 in Memo Report: Population PK and population PKPD analysis of nintedanib in pediatric patients with fibrosing Interstitial Lung Disease
The solid lines represent the mean (expectation of) the typical %predicted FVC difference from placebo at 24 and 52 weeks versus $C_{trough,ss}$ and the shaded areas represent the 90% confidence interval based on 2000 SIR replicates. The black filled circle indicates the median $C_{trough,ss}$ in the presented group, and the dashed gray line indicates the observed 5th and 95th percentiles of $C_{trough,ss}$. The red filled circle indicates the median EC_{80}, and the dashed red line indicates the 90% confidence interval of EC_{80}, based on 2000 SIR replicates. The horizontal, solid grey line marks no difference from placebo.

The starting point of the model development for FVC Z-score was a model that was previously developed based on FVC Z-score data from adult patients included in TOMORROW, INPULSIS I, INPULSIS II, SENSCIS and INBUILD. This model consisted of a linear placebo model and an Emax model to describe the relationship between nintedanib Ctrough,ss and FVC Z-score response.

The population PKPD model parameter estimates of the base FVC Z-score model are presented in Table 27, in comparison to the external evaluation model.

Table 27: Parameter estimates of the base FVC Z-score PKPD model, in comparison to the FVC Z-score external evaluation model.

		Base model			External evaluation model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
Baseline	Z-score	-3.45	8.96		-1.86		
Slope*	Z-score/year	-0.310	7.94		-0.309		
E_{max}*	Z-score/year	0.271	92.6		0.324		
EC_{50}*[a]	nM	4.90	528		10.4		
IIV Baseline	SD, Z-score	1.92	11.4	0	1.16		0
IIV Slope*	SD, Z-score/year	0.381	2.21	7.92	0.380		0
IIV RUV	CV	0.292	22.8	13.6	0.416		12.0
Add. RUV	Z-score	0.264	7.28	4.97	0.176		0

OFV of Base model and External evaluation model cannot be compared: the OFV of the Base model includes the prior information and the OFV of the External evaluation model is based only on analysis data.
* For the base model, supported by adult priors.
[a] For the base model, EC_{50} ended up at the lower boundary and the RSE for this parameter therefore is not reliable.
Source: Table 18 in Pop PK and pop PKPD for nintedanib in pediatric patients with fibrosing interstitial lung disease (c37084509-03)

The parameter estimates of the final FVC Z-score model are presented in Table 28, in comparison to the base model.

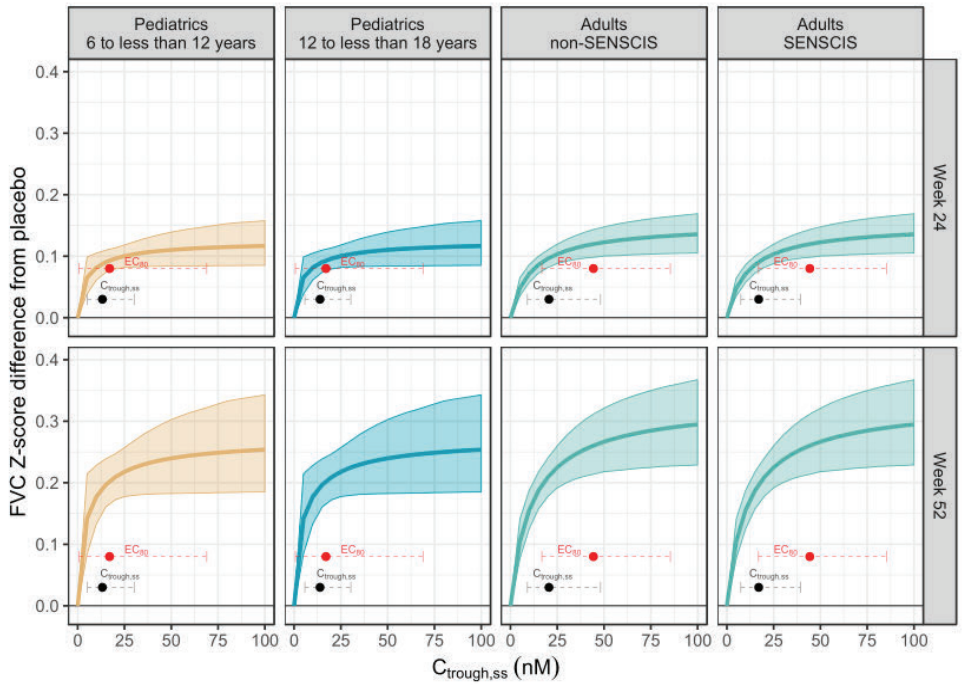
Table 28: Parameter estimates of the final FVC Z-score model, in comparison to the base FVC Z-score model

		Final model			Base model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
Baseline	Z-score	-3.47	8.82		-3.45	8.96	
Slope*	Z-score/year	-0.309	4.65		-0.310	7.94	
E_{max}*	Z-score/year	0.310	24.4		0.271	92.6	
EC_{50}*[a]	nM	9.30	75.3		4.90	528	
Pediatric change in Slope[b]	Z-score/year	0.219	44.8				
Pediatric age on IIV Slope	rel. change per yoa	-0.0720	57.7				
IIV Baseline	SD, Z-score	1.92	11.4	0	1.92	11.4	0
IIV Slope*	SD, Z-score/year	0.379	2.20	15.8	0.381	2.21	7.92
IIV RUV	CV	0.294	22.5	13.4	0.292	22.8	13.6
Add. RUV	Z-score	0.257	7.32	5.17	0.264	7.28	4.97

* supported by adult priors.
[a] For the base model, EC_{50} ended up at the lower boundary and the RSE for this parameter therefore is not reliable. For the final model the estimate returned closer to the mode of the adult prior.
[b] Translating into a Slope of -0.0901 Z-score/year for a pediatric patient.
Source: Table 20 in Pop PK and pop PKPD for nintedanib in pediatric patients with fibrosing interstitial lung disease (c37084509-03)

The model estimated ER relationship of FVC z-score is depicted in Figure 13.

Figure 13: Typical population predictions of FVC Z-score difference from placebo versus $C_{trough,ss}$ for the final FVC Z-score model, stratified by age group and by study for adults



Source: Figure 63 in Memo Report: Population PK and population PKPD analysis of nintedanib in pediatric patients with fibrosing Interstitial Lung Disease

The solid lines represent the mean (expectation of) the typical FVC Z-score difference from placebo at 24 and 52 weeks versus $C_{trough,ss}$ and the shaded areas represent the 90% confidence interval based on 2000 SIR replicates. The black filled circle indicates the median $C_{trough,ss}$ in the presented group, and the dashed gray line indicates the observed 5th and 95th percentiles of $C_{trough,ss}$. The red filled circle indicates the median EC_{80}, and the dashed red line indicates the 90% confidence interval of EC_{80}, based on 2000 SIR replicates. The horizontal, solid line marks no difference from placebo.

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