12 December 2024
EMA/2963/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ofev

International non-proprietary name: nintedanib

Procedure No. EMEA/H/C/003821/X/0057/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABCA3	ATP binding cassette subfamily A member 3
ATP	Adenosine triphosphate
bid	bis in die (twice daily dosing)
C3 M	Type III collagen metabolite
CA-125	Cancer-Antigen 125
chILD	Childhood interstitial lung disease
cHP	Chronic hypersensitivity pneumonitis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRP	C-reactive protein
CSF1R	Colony-stimulating factor 1 receptor
CTD	Common technical document
CTR	Clinical trial report
DBL	Database lock
DILI	Drug induced liver injury
DLCO	Diffusing capacity of the lung for carbon monoxide
DM	Dermatomyositis
EC	European Commission
FGFR	Fibroblast growth factor receptor
FVC	Forced vital capacity
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HRCT	High-resolution computed tomography
HSCT	Haematopoietic stem cell transplant
ICH	International Council for Harmonisation
IL	Interleukin
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
KL-6	Krebs von den Lungen-6
Lck	Lymphocyte-specific tyrosine-protein kinase
LDH	Lactate dehydrogenase
Lyn	Tyrosine-protein kinase Lyn

MAP	Meta-analytic predictive
MCTD	Mixed connective tissue disease
MO	Major Objection
MMRM	Mixed model with repeated measurements
6MWT	6-minute walk test
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
NSIP	Non-specific interstitial pneumonia
PD	Pharmacodynamic(s)
PDGFR	Platelet-derived growth factor receptor
PedsQL™	Paediatric Quality of Life Questionnaire™
PF-ILD	Progressive fibrosing interstitial lung disease
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PM	Polymyositis
PopPK	Population pharmacokinetics
RA	Rheumatoid arthritis
REML	Restricted maximum likelihood
RH	Relative Humidity
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard deviation
SFTPC	Surfactant protein deficiency
SP-D	Surfactant protein D
SpO_2	Oxygen saturation
Src	Proto-oncogene tyrosine-protein kinase
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis associated ILD
TKI	Tyrosine kinase inhibitor
TOEP	Toeplitz matrix
TOEPH	Toeplitz with heterogeneous variances
TS	Treated set

TSE	Transmissible Spongiform Encephalopathy
TSAP	Trial statistical analysis plan
UIP	Usual interstitial pneumonia
UV	Ultraviolet
VEGFR	Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Submission of the dossier

Boehringer Ingelheim International GmbH submitted on 4 October 2023 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to add a new strength of 25 mg hard capsules, grouped with an extension of indication (C.I.6.a) to include treatment of fibrosing Interstitial Lung Diseases (ILDs) in children and adolescents from 6 to 17 years of age for Ofev, following the assessment of procedure X/0052/G, based on final results from study 1199-0337 (A Double Blind, Randomised, Placebo-controlled Trial to Evaluate the Dose-exposure and Safety of nintedanib Per os 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), which is supplemented by the currently ongoing prospective Phase III extension trial 1199-0378 (An Open-label Trial of the Long-term Safety and Tolerability of Nintedanib Per os, on Top of Standard of Care, Over at Least 2 Years, in Children and Adolescents With Clinically Significant Fibrosing Interstitial Lung Disease). The main objective of the study 1199-0337 was to evaluate dose-exposure and safety of nintedanib in children and adolescents with fibrosing Interstitial Lung Disease (ILD). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 12.0 of the RMP has also been submitted.

The MAH applied for an addition of a new strength.

The MAH applied for the following indication for Ofev 25 mg tablets:

“Treatment of fibrosing interstitial lung diseases (ILDs) in children and adolescents from 6 to 17 years old”.

Previous interaction with EMA and CHMP

This is resubmission of the application originally submitted in 2022. On 09 February 2023, following the Day 120 request for supplementary information, the MAH withdrew the extension application and requested to change the scope of the variation from a type II variation classification C.1.6.a (extension of indication) to a type II variation classification C.1.4, with the purpose of updating the product information to reflect the paediatric data obtained in trial 1199-0337. Now this application is resubmitted as a line extension grouped with an extension of indication.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0150/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0150/2019 was completed.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Finbarr Leacy Co-Rapporteur: Ewa Balkowiec Iskra

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	4 October 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 January 2024
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	23 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 January 2024
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	01 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 February 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 February 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to	11 July 2024

CHMP during the meeting on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 July 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	25 July 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	19 August 2024
The PRAC Rapporteur circulated the preliminary Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 August 2024
The CHMP Rapporteur circulated the preliminary Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 September 2024
The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 September 2024
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	19 September 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	14 October 2024
The PRAC Rapporteur circulated the preliminary Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	22 October 2024
The CHMP Rapporteur circulated the preliminary Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	30 October 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2024
SAG convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	05 November 2024
The CHMP Rapporteur circulated the updated Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	07 November 2024
The CHMP agreed on a 3rd list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	14 November 2024
The MAH submitted the responses to the 3rd CHMP List of Outstanding	19 November 2024

Issues on	
The CHMP and PRAC Rapporteur circulated the joint preliminary Assessment Report on the responses to the 3rd List of Outstanding Issues to all CHMP and PRAC members on	27 November 2024
The CHMP and PRAC Rapporteur circulated the joint updated Assessment Report on the responses to the 3rd List of Outstanding Issues to all CHMP and PRAC members on	05 November 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ofev on	12 December 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Childhood interstitial lung disease (chILD) comprises a complex and heterogeneous spectrum of rare respiratory disorders, which affect infants, children, and adolescents and are associated with varying clinical course and prognosis.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Overall, the prevalence of paediatric interstitial lung diseases is substantially lower than in adults. As there are no formal studies in children, only scarce numbers on chILD prevalence and incidence are available for children from 0 up to 18 years of age, comprising prevalences of 3.6 per million (0 to 16 years) in UK and Ireland (1995-1998) and an incidence of 1.3 per million (0 to17 years) in Germany (2005-2006). Data on the natural history of chILD are limited. However, similar to a subset of adults with interstitial lung diseases (ILDs) who develop a progressive phenotype characterised by worsening symptoms, lung function decline, increased morbidity, and early mortality, some paediatric patients with ILD also develop chronic lung fibrosis. Available data from the UK and France suggest that progressive fibrosis occurs in 2% to 7% of patients with chILD. A subgroup of children with fibrosing ILD experiences significant morbidity and mortality. Data from 99 paediatric ILD patients in the age range of 1 month to 18 years suggested that the 2-, 4-, and 5-year survival rates were 83%, 72%, and 64%, respectively. Progressive fibrosing ILD based on worsening radiological findings or decline in forced vital capacity (FVC) has been observed e.g. in children with surfactant protein deficiency (SFTPC) mutations, connective tissue disease-associated ILD, hypersensitivity pneumonitis, and radiation-induced lung injury.

2.1.3. Aetiology and pathogenesis

Both in adults and children, the pathogenesis of fibrosing ILD involves tissue damage resulting in the release of fibrogenic growth factors, fibroblast proliferation and transformation to myofibroblasts, excess deposition of extracellular matrix and aberrant remodelling of the lung architecture. This

injurious process can occur both in children and in adults. It is not clear whether the mechanisms of fibrosis in adults and children with ongoing alveolarisation are the same. It has been postulated that in the context of lung growth and development in paediatric patients with ILD, processes are in place to help counteract the fibrotic process. Nonetheless, there are paediatric patients presenting with clinically significant fibrosing ILD.

2.1.4. Clinical presentation, diagnosis

Although some ILDs (such as rheumatoid arthritis [RA]-ILD) can occur in both children and adults, certain ILDs occur more frequently in children (such as surfactant protein deficiency disorder) while others are almost exclusively found in adults (such as idiopathic pulmonary fibrosis [IPF]). As a result, the composition of the clinical diagnoses associated with lung fibrosis in paediatric patients, though overlapping, differs from that seen in adults. ILDs in children are often classified as disorders more prevalent in infancy (such as growth abnormalities or surfactant protein deficiency), disorders not specific to infancy (such as those related to systemic disease processes or an impaired immune system) and unclassifiable disorders. Algorithms designed to facilitate the categorisation of chILD have been proposed. Potential paediatric conditions likely to be associated with clinically significant fibrosing ILD include, but are not limited to, the following:

- Surfactant protein deficiency (SFTPC and adenosine triphosphate [ATP] binding cassette subfamily A member 3 [ABCA3] mutations);
- Chronic hypersensitivity pneumonitis (cHP);
- Toxic/radiation/drug-induced pneumonitis;
- Post-haematopoietic stem cell transplant (HSCT) fibrosis;

Childhood ILD comprises more than 200 rare and heterogenous conditions which are characterised by inflammatory and fibrotic changes to the lung parenchyma. The composition of the clinical diagnoses associated with lung fibrosis in paediatric patients partly overlaps with that seen in adults, with ILDs occurring less frequently in children than in adults. The pathophysiology of chILD is believed to involve a genetic component together with exposure-related injury or autoimmune dysregulation. ILD may present shortly after birth, with unexplained respiratory stress. Later presentations may include non-specific respiratory symptoms (such as dyspnoea or dry cough), crackles, digital clubbing, respiratory failure, exercise intolerance and diffuse abnormalities on HRCT. Among 191 biopsy-proven cases of ILD in children aged 2 to 18 years, 63% presented with cough, 57% with exercise intolerance and 54% with dyspnoea. Worsening of radiological findings or decline in FVC has also been observed in children with ILD.

Lung function trajectories throughout the course of life generally comprise 3 phases: a growth phase throughout childhood and early adulthood, a plateau phase, and a phase of decline with aging. In children with ILD, lung growth means that lung function and volume may stagnate or even increase while overall the ILD is worsening at the same time.

Children with ILD may experience acute exacerbations characterised by worsening of symptoms, lung function, or radiological abnormalities. In rare cases, paediatric patients with fibrosing ILD may have to be hospitalised because of a respiratory-related event.

2.1.5. Management

Currently, there are no approved therapies for the treatment of fibrosing ILD in children or adolescents.

2.2. About the product

Mode of action

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. In addition, nintedanib inhibits Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn), Src (proto-oncogene tyrosine-protein kinase src), and CSF1R (colony stimulating factor 1 receptor) kinases. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signalling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in interstitial lung diseases.

Nintedanib inhibits the differentiation and migration of fibrocytes, and the migration, proliferation, and contraction of fibroblasts. By reducing the number of fibroblasts and their transformation to myofibroblasts, the secretion of extracellular matrix is reduced. Furthermore, nintedanib blocks the differentiation of alternatively activated macrophages and the release of profibrotic mediators from T cells involved in the initiation of fibrosis.

Placebo-controlled clinical trials have demonstrated a consistent effect of nintedanib on reducing the rate of decline in FVC in adult patients with idiopathic pulmonary fibrosis (IPF), other progressive fibrosing ILDs (PF-ILDs), and ILD associated with systemic sclerosis (SSc-ILD). The risks of treatment with nintedanib in adult patients are related predominantly to the gastrointestinal tract (diarrhoea, vomiting, nausea, abdominal pain, pancreatitis) and to the hepatobiliary system (increases in hepatic enzymes and bilirubin, including drug-induced liver injury [DILI]). They are typically managed with symptomatic therapy, dose reduction from 150 mg bid to 100 mg bid, or treatment interruption, without the need for permanent discontinuation of treatment in the majority of patients.

Nintedanib (Ofev®), 100 mg and 150 mg soft capsules, has been approved as treatment for adult patients with IPF, other chronic fibrosing ILDs with progressive phenotype, and SSc-associated ILD. It was first approved in the USA on 15 Oct 2014 and in the EU/EEA on 15 Jan 2015.

In the EU, nintedanib (Vargatef®) is also approved in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy. It was first authorised for the treatment of NSCLC on 21 Nov 2014.

Pharmacological classification

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX09

Claimed indication and recommendation for use and posology

The originally proposed indication for nintedanib (Ofev) in the EU was ‘Treatment of fibrosing interstitial lung diseases (ILDs) in children and adolescents from 6 to 17 years’.

The indication was amended subsequently by the MAH to: Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant progressive fibrosing interstitial lung diseases (ILDs). The final recommended indication is now

Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs).

Ofev is indicated in adolescents and children aged 6 years and older for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

The proposed posology for children and adolescents

The recommended single dose of nintedanib is administered twice daily, approximately 12 hours apart. Ofev is for oral use. The capsules should be taken with food, swallowed whole with water, and should not be chewed. The capsule should not be opened or crushed.

The recommended dose of Ofev for paediatric patients aged 6 to 17 years of age is based on the patient's weight (Table 1). The dose should be adjusted according to weight as treatment progresses.

Nintedanib has not been studied in patients with a weight below 13.5 kg and therefore, it is not recommended in this population. Treatment should be interrupted in case the patient experiences a weight decrease below 13.5 kg. Treatment can be resumed when the patient's weight reaches the threshold of 13.5 kg. Ofev is not recommended for patients below 6 years of age.

For specific dose reduction recommendations for the management of adverse reactions in paediatric population, see Table 1.

Table 1: Ofev dose and dose reduction recommendation in milligrams (mg) by body weight in kilograms (kg) for paediatric patients aged 6 years to 17 years old

Weight range in kilograms (kg)	Ofev dose in milligrams (mg)	Ofev dose reduction recommendation in milligrams (mg)
13.5 - 22.9 kg	50 mg twice daily	25 mg twice daily
23.0 - 33.4 kg	75 mg twice daily	50 mg twice daily
33.5 - 57.4 kg	100 mg twice daily	75 mg twice daily
57.5 kg and above	150 mg twice daily	100 mg twice daily

Strengths requiring combination of more than one capsule (see section 5.2):

50 mg: Two 25 mg capsules

75 mg: Three 25 mg capsules

100 mg: One 100 mg capsule or four 25 mg capsules

150 mg: One 150 mg capsule or six 25 mg capsules

2.3. Type of Application and aspects on development

Development programme

The clinical development programme to support the use of nintedanib for the proposed indication consists of a single, prospective Phase III clinical trial 1199-0337 (InPedILD; ClinicalTrials.gov NCT04093024; EudraCT 2018-004530-14).

As the conduct of a confirmatory efficacy trial was deemed not feasible based on the low disease prevalence in children, a focused pharmacokinetic (PK) and safety evaluation of nintedanib in paediatric patients in the age range of 6 to 17 years with clinically significant fibrosing ILD was planned to determine appropriate paediatric dosing of nintedanib in children and adolescents. To facilitate interpretation of the trial, additional statistical extrapolation analysis methods that leverage data collected in adults, including Bayesian analysis methods with informative priors, were prospectively planned.

Due to the low prevalence of chILD, a basket approach, similar to the one used in the adult development programme for PF-ILDs other than IPF, was used in trial 1199-0337. It grouped together children and adolescents with different underlying clinical diagnoses of fibrosing ILDs (such as surfactant protein deficiency, cHP, toxic/radiation/drug-induced pneumonitis, HSCT fibrosis, and connective tissue disease related disorders) based on the similarity in the pathophysiology of their disease in fibrotic remodelling. Supportive data on efficacy in the proposed paediatric programme were collected to support inferences of clinical benefit and evaluation of the benefit-risk of nintedanib in the target population. The present submission is based on all data from trial 1199-0337.

Patients receiving trial medication until the end of the trial were offered participation in a separate open-label extension trial 1199-0378 which was initiated on 04 Apr 2022 after confirmation of a positive benefit-risk assessment based on database lock (DBL) 1 of trial 1199-0337. This extension trial is planned to collect additional safety and efficacy data for at least 2 years.

2.4. Quality aspects

2.4.1. Introduction

This line extension concerns the addition of this new strength to the previously approved 100 mg and 150 mg soft capsule strengths. As part of the extension the indication is also extended to a paediatric patient population.

The finished product is presented as soft capsules containing 25 mg of nintedanib (as esilate).

The other ingredients are:

Capsule content: triglycerides medium-chain, hard fat, lecithin (soya) (E322)

Capsule shell: gelatin, glycerol (85%), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172)

Printing ink: shellac, iron oxide black (E172), propylene glycol (E1520)

The product is available in HDPE bottles with screw cap and aluminium/aluminium perforated unit dose blisters as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substance documentation is identical to that previously approved for the authorised strengths and is acceptable. No new information has been provided.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The 25 mg finished product is an orange-coloured, opaque, oval soft-gelatin capsule (approx. 8 x 5 mm) imprinted on one side in black with “25”. The qualitative and quantitative composition is provided in the dossier.

The aim of development was to generate a formulation suitable for the intended paediatric population. The same excipients are used as per the approved 100 mg and 150 mg capsules and the development leveraged the knowledge available from the approved formulations. For example, it is known from the authorised capsule strengths that at higher temperatures sedimentation of the capsule contents has been observed, and at increased temperature and humidity the active substance can migrate into the gelatin shell. This knowledge informed for example, the choice of container closure systems and the selected storage conditions. There are no changes to the active substance as compared to the approved strengths. The suitability of the dosage form in the intended paediatric population was considered, a small capsule size was selected that showed high patient acceptability, and the strength chosen enables suitable dosing flexibility. The ability to mix the unbroken capsule with a small amount of food was investigated. The capsules may be given with a small amount of apple sauce or chocolate pudding in accordance with the relevant instructions in the product information.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation used during clinical studies is the same as that intended for marketing. The only difference was the absence of imprinting on the capsule shells. For further information on the clinical studies performed please refer to the clinical section of the report. In addition to the clinical studies, the applicant performed in vitro dissolution characterisation of the 25 mg strength. During these in vitro dissolution comparisons, similarity of dissolution profiles could not be confirmed between all the strengths under all relevant pH testing conditions, in particular at pH 4.5. The applicant did perform a bioequivalence study comparing the 25 mg strength to the approved 100 mg strength. The results of the bioequivalence study were found to be acceptable. The differences observed regarding in vitro dissolution are therefore of no relevance to the in vivo behavior.

The discriminatory power of the dissolution method intended for quality control purposes has been demonstrated.

With respect to the manufacturing process development, the knowledge from the approved strengths was leveraged. The process uses the same capsule fill mix as is used for the approved strengths, only the capsule size and markings differ. The process development therefore focused on any optimisation and development of the encapsulation process. The applicant developed an acceptable process capable of producing the 25 mg capsules at the intended commercial batch size and has considerable experience in the manufacture of these batches and from the manufacture of the other approved strengths.

The primary packaging is aluminium/aluminium blisters of HPDE bottles, the material comply with Ph. Eur. and EC requirements where relevant. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

Satisfactory GMP documentation has been provided concerning the relevant manufacturing site(s).

The manufacturing process consists of eight main steps: fill mix preparation, gelatin mass preparation, encapsulation, drying, size sorting, washing, printing and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by the production of three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications, includes appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC/UV), dissolution (UV/VIS), uniformity of dosage units (Ph. Eur.), assay (HPLC/UV), and degradation products (HPLC/UV).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

With respect to nitrosamine impurities the originally provided assessment by the applicant could not be accepted, this assessment had not considered all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). In particular the risk for N-nitroso-desmethyl-nintedanib which could potentially form from the active substance had not been accounted for. A major objection (MO) was raised on this aspect and maintained during the procedure. The applicant was requested to update their risk assessment and provide data demonstrating the acceptable intake for N-nitroso-desmethyl-nintedanib would not be exceeded. The applicant resolved the major objection by updating their nitrosamines risk assessment in line with the latest available guidance and by providing analytical testing data for N-nitroso-desmethyl-nintedanib. The analytical data suitably demonstrated that this potential impurity is not present at levels greater than 10% of the acceptable intake in the finished product. Data for 8 finished product batches of the 25 mg strength and 5 batches of the already approved 150 mg strength were provided to support this position. The analytical method used to support the testing was suitably validated. Based on the updated information provided in the response to the MO, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 18 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH), for 12 months at intermediate conditions (30°C/75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. For the HDPE bottle presentation a bracketing approach was taken to consider the minimum (60 tablet) and maximum (180 tablet) container fill.

Samples were tested for appearance, dissolution , assay , degradation products , and microbiological quality (Ph. Eur.). The analytical procedures used are stability indicating. At all conditions the assay and impurity values remain within specifications and show little change from the initial time-point. At the accelerated conditions the dissolution results were impacted and the product did not meet the specification, and a softening of the capsules was observed. This was less pronounced at the intermediate condition where only a slight decrease in dissolution and capsule hardness was observed. Due to the softening effect on the capsules at increased temperatures it is recommended that the storage is restricted to at or below 25 ºC and to be protected from moisture.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No sensitivity to light was observed.

In-use stability data for the HDPE bottles has been generated for one primary stability batch covering a period of up to 60 days following 10 months storage at long-term conditions (25°C/60 % RH). This time period corresponds to twice the actual treatment period needed for a 60 count bottle, and the

bottle used represents the extreme configuration regarding humidity impact due to the largest headspace. The available stability data including the in-use stability data demonstrates that a specific in-use shelf-life is not needed for the HDPE bottles.

Based on available stability data, the proposed shelf-life of 24 months in the original package to protect from moisture at or below 25 °C as stated in the SmPC are acceptable.

2.4.3.5. Adventitious agents

Gelatin obtained from swine sources is used in the finished product composition. It was confirmed that the swine sources are from healthy animals fit for human consumption.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure one MO concerning quality aspects was raised, this concerned the risk assessment provided for nitrosamine impurities and the need for data related to the potential nitrosamine impurity N-nitroso-desmethyl-nintedanib. To resolve this MO the applicant updated their nitrosamine risk assessment and provided analytical testing data for the finished product demonstrating that there is no risk of nitrosamine impurities considering the relevant acceptable intakes.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

In the original MAA the toxicity profile of nintedanib was explored in both mice (up to 13 weeks) and rats (up to 26 weeks). The most prominent treatment related findings which were considered to be related to the pharmacodynamic activity of nintedanib as a VEGFR-2 inhibitor were: dentopathies of the continuously growing incisors which in turn contributed to the lower body weight and body weight gains observed; the thickening of the growth plates in long bones; PAS-positive hyaline intracytoplasmic granules in podocytes and glomerular endothelium of the glomeruli of the kidneys; the reduced size/increased number of corpora lutea and presence of luteinized follicles in the ovaries; and lastly cellular depletion of the bone marrow which may be related to the various roles VEGF has in

hematopoiesis. Changes in growing bones were reversible after discontinuation, while alterations in tooth structure and function were irreversible.

Therefore, the potential identified risks with respect to the preclinical data are potential skeletal toxicity and potential toxicity on teeth development.

In the line with the initial nintedanib PIP (EMEA-001006-PIPI05-18), the existing nonclinical studies are considered adequate to support clinical studies in the paediatric population and the agreed PIP did not contain any non-clinical measures. Therefore, with this application no additional nonclinical reports or literature is provided.

The MAH has submitted a justification for the absence of an updated environmental risk assessment (ERA).

It is agreed with the MAH that the effects on the environment by adding another indication are considered to be negligible and well covered by the Fpen used and that the ERA initially assessed. The previous assessment and conclusion remains valid for the current type II variation covering the additional indication in children with ILD.

2.5.2. Ecotoxicity/environmental risk assessment

The MAH has not submitted any additional ERA studies/data with this application.

The applicant's justification that as the PEC in the initial MAA submission was based on an Fpen which was not refined, it represents a worst-case scenario is considered acceptable. The dose used for initial PEC calculations (500 mg) is in excess of the max dose proposed for use with the current indication. The initially calculated PEC exceeded the action limit and phase II and IIa studies were conducted and assessed during initial authorisation. Following assessment of these data, nintedanib is not expected to pose a risk to the environment. The extension of indication in the paediatric population represents a very low prevalence and will not impact this conclusion.

2.5.3. Discussion on non-clinical aspects

In this application, no additional non-clinical reports or literature is provided.

The risks based on the preclinical data submitted at time of the initial authorisation are potential skeletal and teeth development toxicities.

Nintedanib is already used in existing marketed products and no significant increase in environmental exposure is anticipated for the new population. Therefore, nintedanib is not expected to pose a risk to the environment.

2.5.4. Conclusion on non-clinical aspects

There are no non-clinical issues precluding the authorisation of the proposed line extension grouped with an extension of indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	**Study No. [Document No.]**	**Objectives of the Study**	**Study Design and Type of Control**	**Test Products; Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
Safety (also PK)	1199-0337 [c35674886-03]	To evaluate dose-exposure and safety of nintedanib in children and adolescents with fibrosing ILD	Phase III trial with a randomised, placebo-controlled, double-blind part comparing nintedanib with placebo (2:1), followed by an open-label part with active treatment	Study drug: nintedanib Soft gelatine capsules 150 mg (or 6x25 mg) bid; 100 mg (or 4x25 mg) bid; 75 mg (3x25 mg) bid; 50 mg (2x25 mg) bid; Oral administration Dosage according to weight bin; reduction to next lower dose possible (with 1x25 mg bid as reduced doses for 50 mg bid) Control drug: placebo Matching soft gelatine capsules, bid, oral administration	Double-blind period: Nintedanib: Entered: 26 Treated: 26 Placebo: Entered: 13 Treated: 13 Open-label period: Nintedanib/ nintedanib: Entered: 21 Treated: 21 Placebo/ nintedanib: Entered: 11 Treated: 11	Paediatric patients with clinically significant fibrosing ILD aged 6 to 17 years	Double-blind period: 24 weeks nintedanib or placebo (2:1) on top of SOC. Open-label period: Nintedanib treatment on top of SOC for a variable length of time	Completed; full CTR
Safety	1199-0378 [data on file]	To assess the safety and tolerability of long-term treatment with nintedanib in paediatric patients with clinically significant fibrosing ILD	Phase III open-label trial with no randomisation	Study drug: nintedanib Soft gelatine capsules 150 mg (or 6x25 mg) bid; 100 mg (or 4x25 mg) bid; 75 mg (3x25 mg) bid; 50 mg (2x25 mg) bid; Oral administration Dosage according to weight bin; reduction to next lower dose possible (with 1x25 mg bid as reduced doses for 50 mg bid)	Rollover patients from trial 1199-0337: Entered: 30 Treated: 30 New patients in trial 1199-0378: Entered: 9 Treated: 9	Paediatric patients with clinically significant fibrosing ILD aged 6 to 17 years	Nintedanib treatment on top of SOC for a variable length of time with at least 2 years for roll-over patients	Ongoing (data up to snapshot on 31 May 2023 are pooled with data from trial 1199-0337 [c42676839-03; c42874679-01])

2.6.2. Clinical pharmacology

2.6.2.1. Introduction

The present application is a re-submission of nintedanib (Ofev) as treatment in paediatric patients with fibrosing interstitial lung diseases (ILDs). The Clinical Pharmacology section includes the previously submitted relative bioavailability study (1199-0463), population PK analysis, the PK/PD analyses for FVC [%pred] and FVC Z-score, and the exposure-safety correlations for diarrhoea and liver enzyme elevation.

2.6.2.2. Pharmacokinetics

Study 1199-0463: Relative bioavailability of 100 mg nintedanib (Ofev®) given as four capsules of 25 mg compared to one capsule of 100 mg following oral administration in healthy male subjects.

This was a single dose, open-label, randomised, two-way crossover trial in healthy male volunteers. Twenty subjects entered the study and 19 were treated and analysed for the bioavailability comparison of the test and reference treatment. In each of the treatment periods, subjects received a dose of 100 mg nintedanib either given as four 25 mg capsules (test treatment, T) or as a single 100 mg capsule (reference treatment, R) immediately after a standard breakfast. The treatments were separated by a wash-out phase of 7 days. Blood samples for the determination of plasma concentrations of nintedanib were drawn up to 72 h after drug intake.

Results of the ANOVA are presented in Table 2. The 90% CIs for the AUC and Cmax ratios were entirely contained within the defined range of 80-125%. Cmax was reached after 4 h (median) for both treatments, indicating that absorption rate between the test and reference treatment were comparable.

Table 2: Adjusted gMeans and relative bioavailability of nintedanib 4*25 mg (Test, T) vs. nintedanib 1*100 mg (reference, R) with subject as random effect - PKS

				Comparison vs nintedanib 1*100 mg (R)				
		Adjusted				90% CI		
PK Parameter/ Treatment	N	gMean	gSE	Ratio (%)	gSE	Lower	Upper	gCV[1] (%)
C_{max} (ng/mL)								29.2
nintedanib 1*100mg (R)	19	15.23	1.11					
nintedanib 4*25mg (T)	19	15.27	1.11	100.29	1.10	85.05	118.24	
AUC_{0-tz} (h*ng/mL)								13.9
nintedanib 1*100mg (R)	19	150.65	1.07					
nintedanib 4*25mg (T)	19	148.34	1.07	98.47	1.05	90.87	106.69	
$AUC_{0-\infty}$ (h*ng/mL)								13.8
nintedanib 1*100mg (R)	19	157.55	1.07					
nintedanib 4*25mg (T)	19	155.85	1.07	98.92	1.05	91.35	107.12	

1 intra-individual gCV

Population PK analysis of nintedanib in paediatric patients with fibrosing Interstitial Lung Disease

The aim of this analysis was to characterize the pharmacokinetics (PK) of nintedanib in children and adolescent patients 6 to less than 18 years of age with documented clinically significant fibrosing ILD.

The analysis is based on paediatric data from the Phase III study InPedILD (1199-0337) and its open-label extension study InPedILD-ON (1199-0378) up to 31 May 2023.

Previous population PK (popPK) analyses, based on data from adult patients with idiopathic pulmonary fibrosis (IPF), systemic sclerosis associated ILD (SSc-ILD) and progressive fibrosing ILDs (PF-ILD) other than IPF were used as prior information to support the paediatric modelling.

The PK analysis included data from 42 paediatric patients with 443 nintedanib concentration measurements. Subject characteristics for the paediatric PK analysis data set are presented by arm and age group in Table 3 and Table 4.

Table 3: Baseline characteristics for the patients in the PK analysis data set, by age group: continuous covariates

	6 to less than 12 years N=14	12 to less than 18 years N=28	Overall N=42
Body weight (kg)			
Mean (SD)	25.6 (10.2)	49.9 (15.8)	41.8 (18.2)
Median (min, max)	22.6 (15.2, 50.0)	48.6 (22.3, 94.9)	41.6 (15.2, 94.9)
Standing height (cm)			
Mean (SD)	129 (14.4)	156 (11.6)	147 (17.9)
Median (min, max)	126 (109, 155)	154 (131, 185)	152 (109, 185)
Age (y)			
Mean (SD)	9.53 (1.71)	15.0 (1.84)	13.2 (3.17)
Median (min, max)	9.93 (6.81, 11.9)	14.9 (12.3, 17.7)	13.2 (6.81, 17.7)
Lactate dehydrogenase (U/L)			
Mean (SD)	290 (106)	228 (70.8)	249 (87.9)
Median (min, max)	288 (95.0, 425)	204 (155, 496)	220 (95.0, 496)

Baseline characteristics and age groups are computed at the very first visit (Section 4.1).

Table 4: Baseline characteristics for the patients in the PK analysis data set, by age group: categorical covariates

	6 to less than 12 years N=14	12 to less than 18 years N=28	Overall N=42
Ethnicity			
Caucasian	12 (86%)	21 (75%)	33 (79%)
Other Asian*	0 (0%)	2 (7.1%)	2 (4.8%)
Black	1 (7.1%)	2 (7.1%)	3 (7.1%)
American Indian/Alaska Native	1 (7.1%)	2 (7.1%)	3 (7.1%)
Missing	0 (0%)	1 (3.6%)	1 (2.4%)
Nintedanib formulation			
25 mg soft capsule	10 (71%)	5 (18%)	15 (36%)
100 mg soft capsule	4 (29%)	18 (64%)	22 (52%)
150 mg soft capsule	0 (0%)	5 (18%)	5 (12%)
ILD diagnosis°			
Pediatric autoimmune ILD	3 (21%)	10 (36%)	13 (31%)
Surfactant Protein Deficiency	4 (29%)	9 (32%)	13 (31%)
Other fibrosing ILD	5 (36%)	5 (18%)	10 (24%)
Toxic/Radiation/Drug Induced Pneumonitis	1 (7.1%)	2 (7.1%)	3 (7.1%)
Chronic hypersensitivity pneumonia	1 (7.1%)	1 (3.6%)	2 (4.8%)
Post HSCT Fibrosis	0 (0%)	1 (3.6%)	1 (2.4%)
Sex			
Male	8 (57%)	10 (36%)	18 (43%)
Female	6 (43%)	18 (64%)	24 (57%)
Systemic sclerosis°			
SSc-ILD	2 (14%)	5 (18%)	7 (17%)
Non-SSc-ILD	12 (86%)	23 (82%)	35 (83%)

* Other Asian: Asian attending a study site located in a country other than China, Korea, Taiwan, India or Japan.
° All SSc-ILD patients were included in Ped. Autoimmune ILD
Numbers represent the number of patients in each category and the corresponding percentage in relation to the total number of subjects as specified in the column header.
Baseline characteristics and age groups are computed at the very first visit (Section 4.1).

Results

The final popPK model for nintedanib plasma concentrations was a one-compartment model with a lag time followed by first-order absorption and a first-order elimination from the central compartment. WT was included as covariate on CL/F and V/F using allometric scaling with fixed exponents of 0.75 and 1, respectively, as well as ethnicity, SSc-ILD, baseline LDH on Frel. In addition, IOV Frel was higher in paediatric patients (increasing magnitude of IOV with decreasing age). IIV terms were supported on V/F, ka and Frel and IOV was included on Frel. The RUV for nintedanib plasma concentrations was described by an additive model on the log-transformed scale (approximately proportional error). All model parameters, except the paediatric age on IOV Frel covariate coefficient and the RUV, were supported by the adult prior. The parameter estimates of the final nintedanib popPK model are presented in Table 5, in comparison to the base model. Figure 1 and Figure 2 present VPC plots for the final nintedanib popPK model.

Table 5: Parameter estimates of the final nintedanib population PK model, in comparison to the base nintedanib population PK model.

		Final model			Base model		
Run		4			3		
OFV		-444.24			-439.48		
Condition number		9.53			9.45		
		Final model			**Base model**		
	Unit	**Value**	**RSE (%)**	**SHR (%)**	**Value**	**RSE (%)**	**SHR (%)**
CL/F[a]*	(L/h)	909	2.31		910	2.30	
V/F[b]*	(L)	1.07E+04	4.31		1.07E+04	4.27	
k_a*	(/h)	2.74	12.4		2.74	11.5	
t_{lag}*	(h)	0.717	3.23		0.717	3.19	
Other ethnicities[c] on F_{rel}*	Fraction change	0.328	13.3		0.329	13.3	
Korean on F_{rel}*	Fraction change	-0.145	36.6		-0.145	36.7	
SSc-ILD on F_{rel}*	Fraction change	-0.140	27.2		-0.140	27.3	
LDH on F_{rel}*		0.00158	17.2		0.00156	17.3	
Pediatric age on IOV F_{rel}	change per yea	-0.0564	41.3				
IIV V*	(CV)	0.310	10.2	24.9	0.310	10.2	24.6
IIV k_a*	(CV)	1.25	8.76	30.7	1.25	8.80	30.7
IIV F_{rel}*	(CV)	0.417	4.02	12.1	0.419	4.01	4.6
IOV F_{rel}*	(CV)	0.310	3.27	9.48	0.334	3.44	4.49
RUV	(CV)	0.392	4.30	14.7	0.396	4.29	14.1

[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

Figure 1: PcVPC of nintedanib concentrations in InPedILD and InPedILD-ON, for the final nintedanib population PK model. Nintedanib concentrations are displayed versus time since most recent dose on a semi-logarithmic scale. The observed data are indicated by open circles. The solid and dashed red lines represent the median, 10th and 90th percentiles of the observations; the red stars indicate that the percentile is outside the predicted CI and the shaded red and blue areas represent the 95% CI of the median, 10th and 90th percentiles predicted by the model. The orange brush border along the x-axis indicates the bins across time.

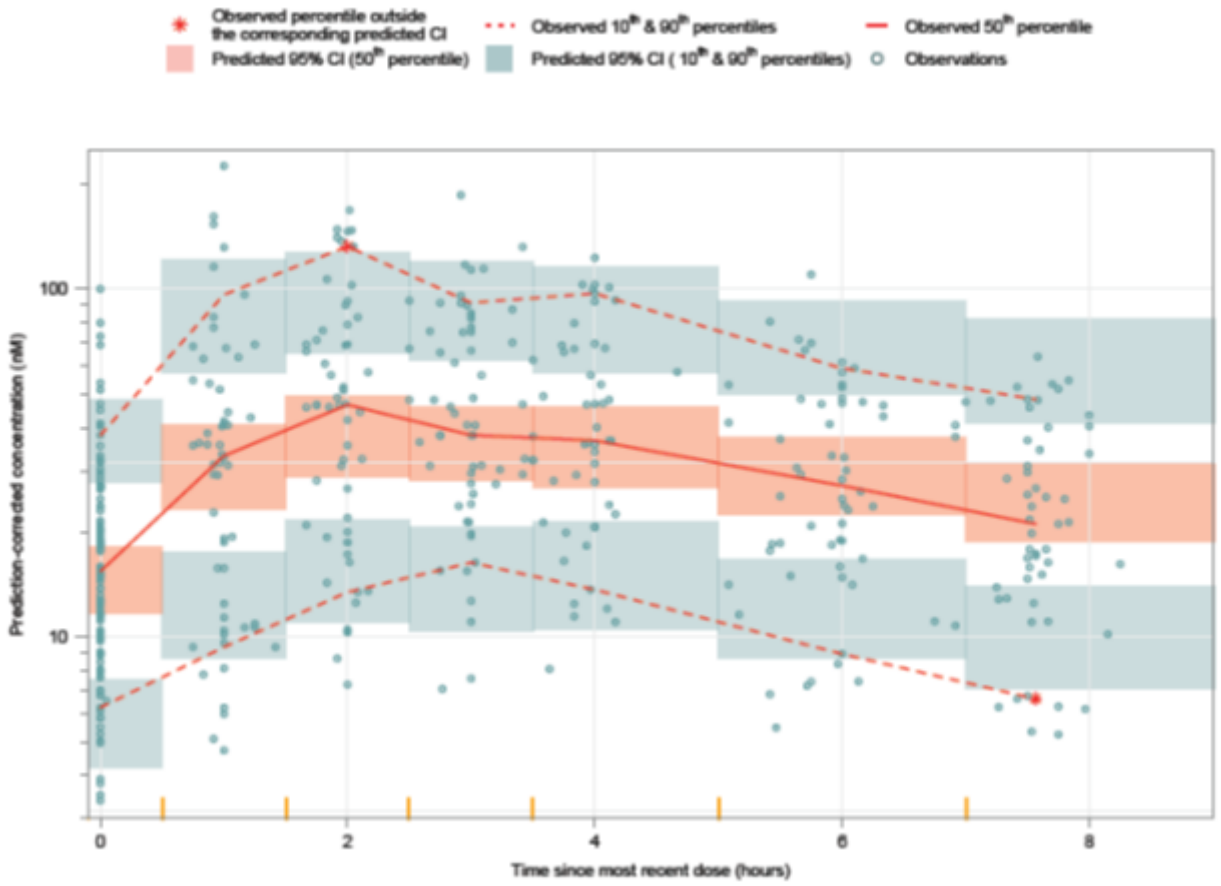
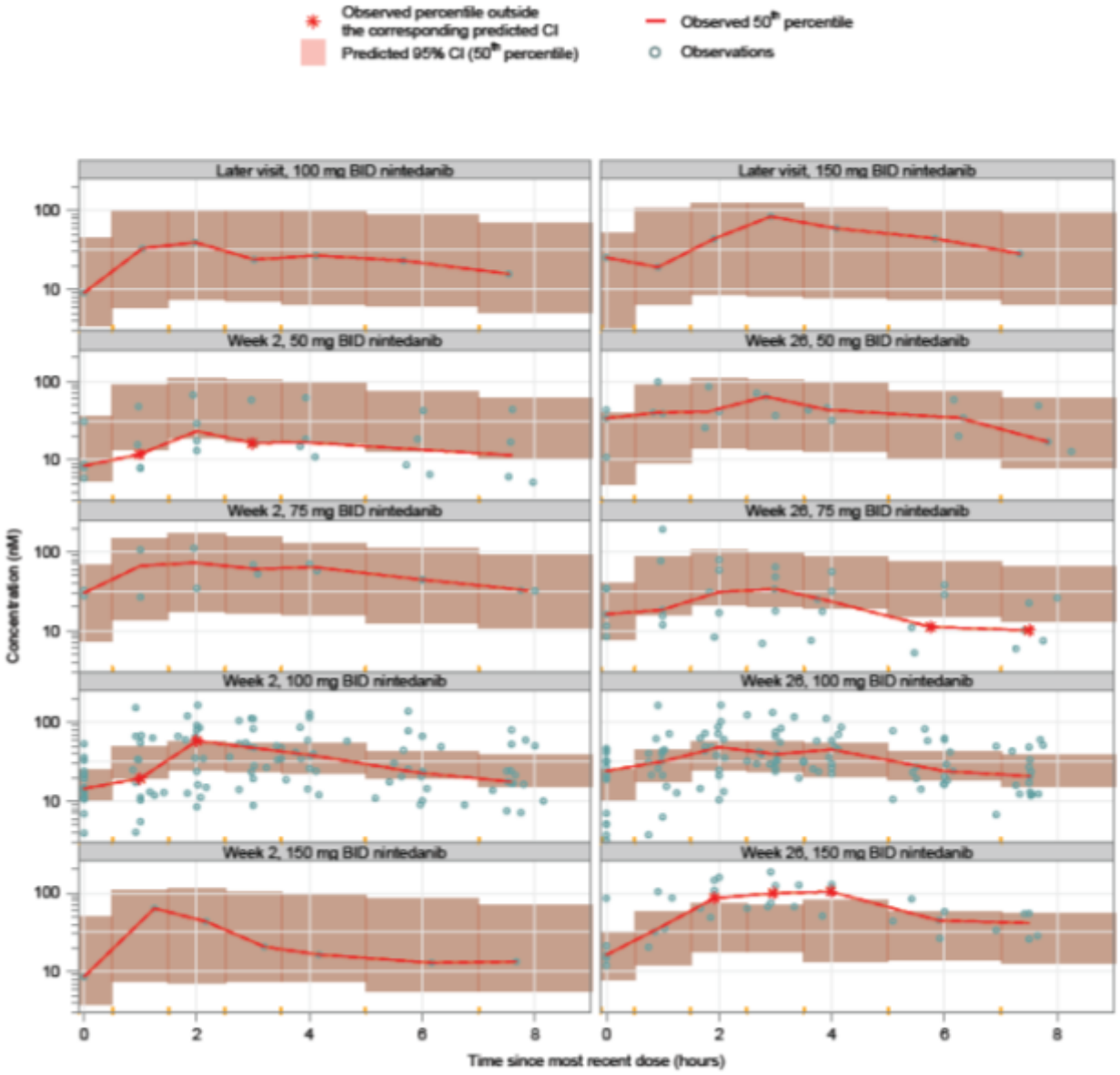


Figure 2: VPC of nintedanib concentrations in InPedILD, stratified by week and actual dose, for the final nintedanib population PK model. Nintedanib concentrations are displayed versus time since most recent dose on a semi-logarithmic scale. The observed data are indicated by open circles. The solid red line represents the median of the observations; the red stars indicate that the percentile is outside the predicted CI and the shaded red areas represents the 95 % CI of the median predicted by the model. The orange brush border along the x-axis indicates the bins across time.



Empirical Bayes estimates of nintedanib exposure

Table 6 displays the summary statistics for EBEs of PK exposure metrics, based on the final popPK model. In this summary table the individually estimated metric (e.g. $AUC_{\tau,ss}$) was taken from Week 2 if randomised to active treatment, whereas for patients initially assigned to placebo, the metric from Week 26 was used instead.

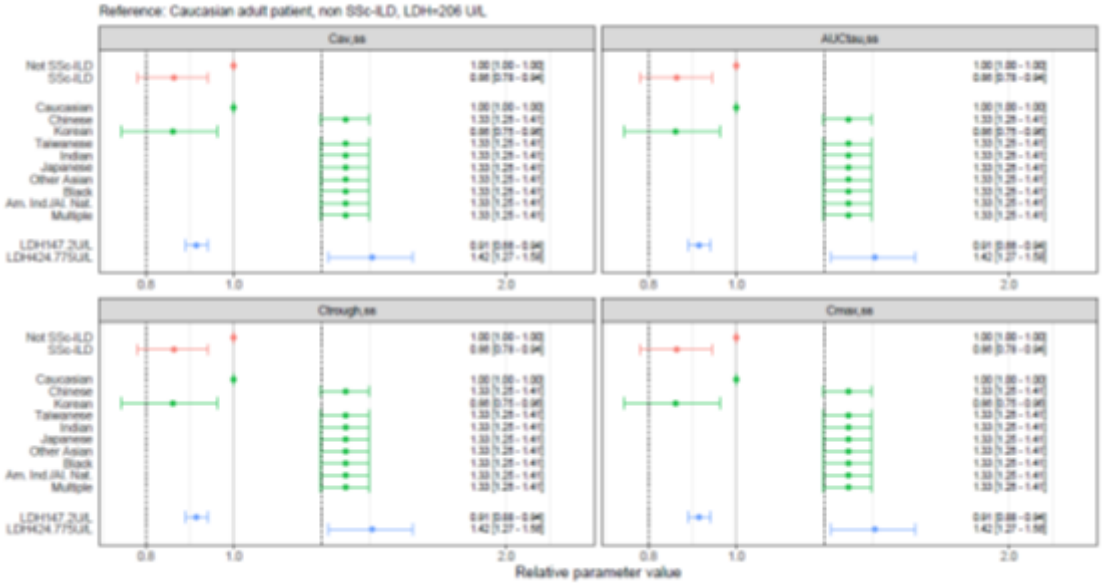
Table 6: PK exposure by paediatric age group, based on the EBEs from the final PK model, at Week 2 (Week 26 for patients initially assigned to placebo), for the patients in the nintedanib PK analysis data set.

Statistic/Age group	$N_{patients}$ (count)	$AUC_{\tau,ss}$ (nM h)	$C_{max,ss}$ (nM)	$t_{max,ss}$ (h)	$C_{trough,ss}$ (nM)
Geometric mean (gCV%)					
6 to less than 12 years	14	368 (34.0)	48.4 (33.7)	1.97 (37.7)	16.5 (40.4)
12 to less than 18 years	28	322 (50.0)	40.7 (49.4)	2.10 (37.0)	15.2 (58.1)
Median (min, max)					
6 to less than 12 years	14	390 (231, 681)	51.8 (28.9, 87.3)	1.81 (1.06, 3.63)	18.7 (9.49, 32.2)
12 to less than 18 years	28	332 (118, 658)	42.9 (12.7, 76.0)	2.02 (1.08, 4.31)	15.0 (5.62, 36.4)

Covariate effects for nintedanib PK

Forest plots for the secondary PK parameters are presented in Figure 3. The effects of body weight are not shown here since this covariate was fixed according to allometric principles.

Figure 3: Forest plots based on the final nintedanib PK model for secondary parameters. Each panel shows the results for one parameter as indicated above the panels. The impact of the covariates is evaluated at the values shown on the y-axis (percentile 2.5% and percentile 97.5% if continuous covariate, or different categories of categorical covariate) and are displayed on a relative scale of the x-axis (showing log-transformed values). The reference set of covariate values, indicated by the vertical solid grey line, is provided in the plot header. The dasher vertical lines indicate the region of 0.8-1.25 relative to the reference set of covariates. The closed symbols represent the median parameter estimates and the whiskers represent the 95% CI based on 2000 SIR replicates. The median and CI limits are provided numerically to the right in each panel. Am.Ind/Al. Nat.: American Indian/Alaska Native.



Simulations of nintedanib PK

For the simulated paediatric population, Caucasian ethnicity was assumed. The LDH level was set to the same level as that observed in adult patients. This was considered as conservative since the 14 children (6 to less than 12 years old) in the analysis data set had higher LDH levels than the adolescent and adult patients. Consequently, this assumption would result in increased deviations from the exposures seen in adults, since the simulated exposure in children (less than 12 years old) was lower than it would have been if using the higher LDH levels that were observed in children. Moreover, SSc-ILD patients were simulated in the same proportions as in the analysis data set. Based on these predictions, it is expected that young children (low-weight children) in particular will have somewhat lower Ctrough,ss, and higher Cmax,ss than adults.

Figure 4 and Table 7 show the simulated PK metrics by WT bins. The WT-based dose adjustment results in less variability in children than observed in adults. The 90% CI in adults shows a wider range of exposures compared to children, with more extreme values for adults at the upper end. However, at the lower end, young children (with low weight) have lower Ctrough,ss than adults with high weight. Compared to the overall geometric mean exposure in adults (without hepatic impairment), the four dose groups in this scenario in the paediatric population are predicted to differ between -17% and -1% for $AUC_{T,ss}$ (and Cav,ss), between +5% and +22% for Cmax,ss, and between -42% and -20% for Ctrough,ss.

Figure 4: Predicted nintedanib $C_{av,ss}$, $AUC_{\tau,ss}$, $C_{trough,ss}$ and $C_{max,ss}$ versus WT bins and stratified by age group, for the PK simulation data set (Caucasian). The blue line is the geometric mean and the blue area spans from the 5th to the 95th percentile, for each WT bin. As reference, the gray area spans from the 5th to the 95th percentile across all adults and the horizontal line indicates the adult geometric mean ($C_{av,ss}$ (red): 26 nM, $AUC_{\tau,ss}$ (orange): 316nM-h, $C_{trough,ss}$ (green): 20 nM, and $C_{max,ss}$ (purple):33 nM). An orange rug (brush border) along the x-axis indicates the lowest WT in each WT bin.

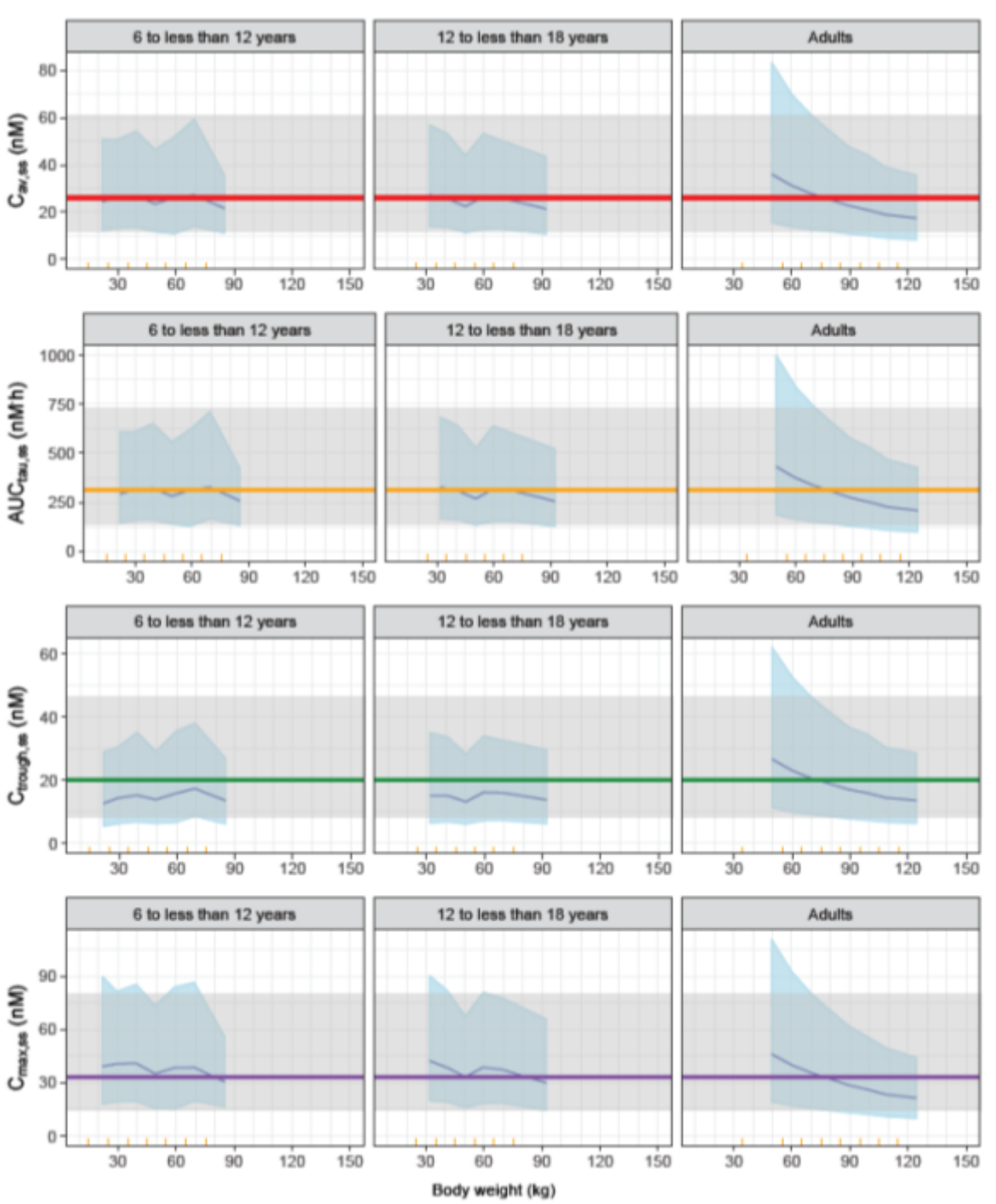


Table 7: Predicted geometric mean (5th and 95th percentiles) for nintedanib PK parameters by WT band for the paediatric subjects in the PK simulation data set (Caucasian)

WT/Regimen	Age[a] (years)	WT[b] (kg)	Fem.[c] (%)	Frac.[d] (%)	$AUC_{t,ss}$[e] (nM·h)*	$C_{av,ss}$[e] (nM)*	$C_{max,ss}$[e] (nM)*	$C_{trough,ss}$[e] (nM)*	$t_{max,ss}$[e] (h)	CL/F[e] (L/h)	V/F[e] (L)
13.5 to <23.0 kg											
50 mg BID	7.00	20.6	51.7	7.15	264 (135, 518)	22.0 (11.2, 43.1)	35.3 (16.9, 75.1)	11.4 (4.95, 24.2)	1.87 (0.963, 3.84)	345 (303, 372)	2940 (2470, 3260)
23.0 to <33.5 kg											
75 mg BID	8.54	27.9	46.1	21.2	314 (156, 617)	26.2 (13.0, 51.4)	40.9 (19.1, 84.8)	14.3 (6.25, 31.0)	1.85 (0.948, 3.92)	432 (381, 489)	3970 (3360, 4680)
33.5 to <57.5 kg											
100 mg BID	12.3	45.8	54.5	40.0	292 (143, 609)	24.4 (11.9, 50.7)	36.5 (16.9, 78.1)	14.3 (6.47, 31.5)	1.87 (0.950, 3.98)	622 (509, 733)	6460 (4940, 8040)
≥57.5 kg											
150 mg BID	14.9	74.8	43.5	31.6	301 (145, 619)	25.1 (12.1, 51.6)	36.0 (16.6, 78.6)	15.8 (7.06, 33.3)	1.88 (0.956, 4.03)	893 (754, 1200)	10500 (8340, 15600)

[a] Mean age for the subjects in each WT band in the PK simulation data set
[b] Mean WT for the subjects in each WT band in the PK simulation data set
[c] Fraction female among the subjects in each WT band in the PK simulation data set
[d] Fraction of subjects for each WT band, in relation to the whole pediatric population used in the simulations
[e] Summarized as geometric mean (5th, 95th percentiles). For the two disposition parameters (CL/F and V/F) values shown are in relation to the population typical F, so that between-subject variability in F is not included.
* Molecular weight of nintedanib: 540 g/mol.

Simulations of nintedanib PK in paediatric patients in Child–Pugh class A - without dose adjustment

For these simulations, all simulated paediatric patients were considered to have chronic liver disease according to Child–Pugh class A (mild hepatic impairment). The adult reference was maintained as before. Figure 5 and Table 8 show the simulated PK metrics by WT bins.

Figure 5: Predicted nintedanib $C_{av,ss}$, $AUC_{\tau,ss}$, $C_{trough,ss}$ and $C_{max,ss}$ versus WT bins and stratified by age group, for the PK simulation data set with Child-Pugh class A, without dose adjustment. The blue line is the geometric mean and the blue area spans from the 5th to the 95th percentile, for each WT bin. As reference, the gray area spans from the 5th to the 95th percentile across all adults (without hepatic impairment) and the horizontal line indicates the adult geometric mean ($C_{av,ss}$ (red): 26 nM, $AUC_{\tau,ss}$ (orange): 316nM·h, $C_{trough,ss}$ (green): 20 nM, and $C_{max,ss}$ (purple):33 nM). An orange rug (brush border) along the x-axis indicates the lowest WT in each WT bin.

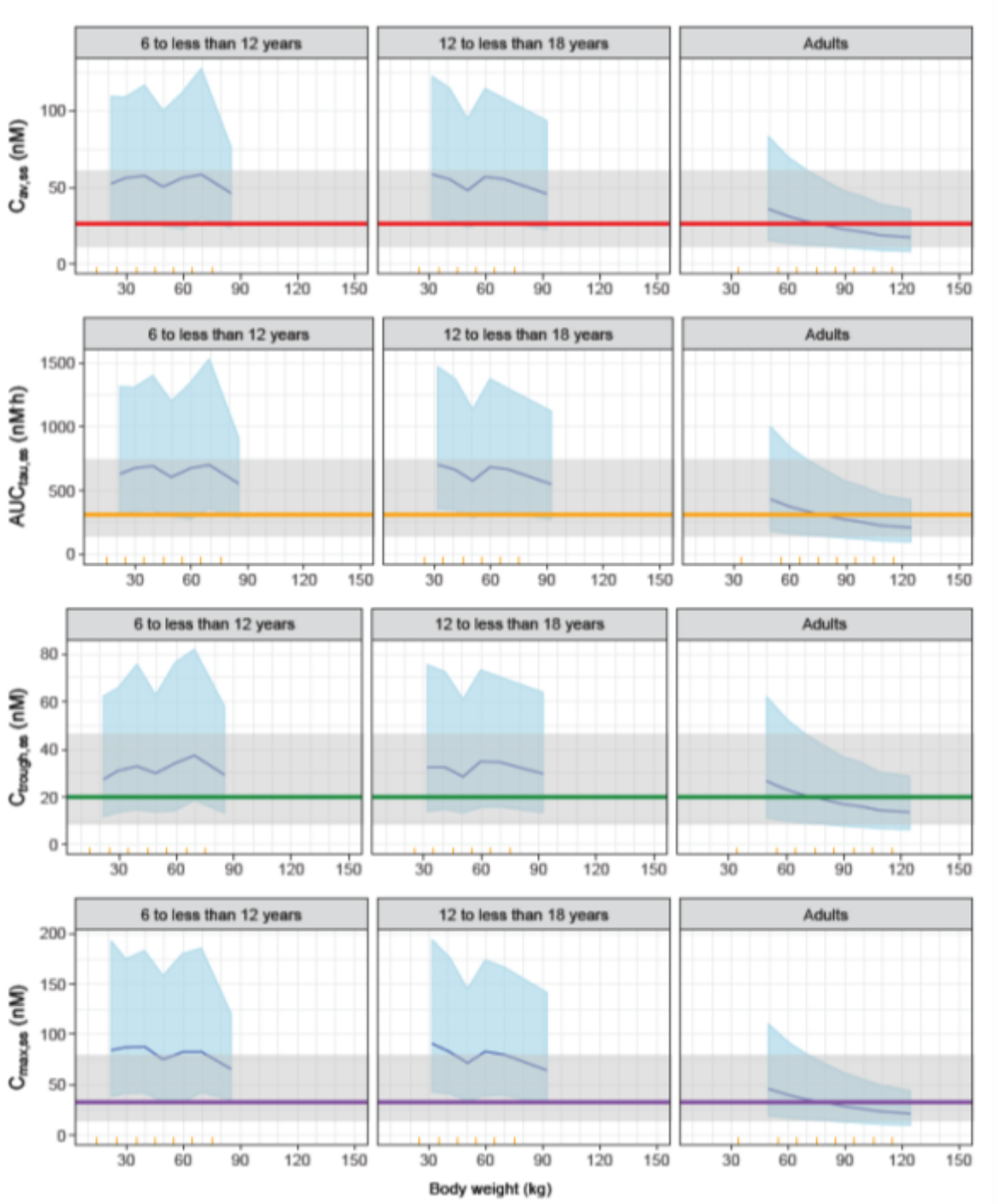


Table 8: Predicted geometric mean (5th and 95th percentiles) for nintedanib PK parameters by WT band for the paediatric subjects in the PK simulation data set with Child-Pugh class A, without dose adjustment.

WT/Regimen	Age[a] (years)	WT[b] (kg)	Fem.[c] (%)	Frac.[d] (%)	$AUC_{\tau,ss}$[e] (nM·h)*	$C_{av,ss}$[e] (nM)*	$C_{max,ss}$[e] (nM)*	$C_{trough,ss}$[e] (nM)*	$t_{max,ss}$[e] (h)	CL/F[e] (L/h)	V/F[e] (L)
13.5 to <23.0 kg											
50 mg BID	7.00	20.6	51.7	7.15	568 (290, 1110)	47.3 (24.2, 92.7)	75.9 (36.3, 162)	24.6 (10.6, 52.0)	1.87 (0.963, 3.84)	345 (303, 372)	2940 (2470, 3260)
23.0 to <33.5 kg											
75 mg BID	8.54	27.9	46.1	21.2	675 (335, 1330)	56.3 (27.9, 111)	87.9 (41.0, 182)	30.7 (13.4, 66.6)	1.85 (0.948, 3.92)	432 (381, 489)	3970 (3360, 4680)
33.5 to <57.5 kg											
100 mg BID	12.3	45.8	54.5	40.0	628 (308, 1310)	52.4 (25.6, 109)	78.5 (36.4, 168)	30.7 (13.9, 67.8)	1.87 (0.950, 3.98)	622 (509, 733)	6460 (4940, 8040)
≥57.5 kg											
150 mg BID	14.9	74.8	43.5	31.6	648 (312, 1330)	54.0 (26.0, 111)	77.4 (35.7, 169)	34.0 (15.2, 71.6)	1.88 (0.956, 4.03)	893 (754, 1200)	10500 (8340, 15600)

[a] Mean age for the subjects in each WT band in the PK simulation data set
[b] Mean WT for the subjects in each WT band in the PK simulation data set
[c] Fraction female among the subjects in each WT band in the PK simulation data set
[d] Fraction of subjects for each WT band, in relation to the whole pediatric population used in the simulations
[e] Summarized as geometric mean (5th, 95th percentiles). For the two disposition parameters (CL/F and V/F) values shown are in relation to the population typical F (without hepatic impairment), so that between-subject variability in F is not included.
* Molecular weight of nintedanib: 540 g/mol.

Based on these predictions, the paediatric population with Child–Pugh class A (mild hepatic impairment), without dose adjustment, can be expected to have higher nintedanib exposures than adults without hepatic impairment. In the paediatric population with Child–Pugh class A, without dose adjustment, each of the nintedanib PK-exposure metrics is expected to be 115% higher than in children without hepatic impairment. Compared to the overall geometric mean exposure in adults (without hepatic impairment), the four dose groups in this paediatric population are predicted to differ between +80% and +114% for AUCτ,ss (and Cav,ss), between +127% and +163% for Cmax,ss, and between +24% and +72% for Ctrough,ss.

Simulations of nintedanib PK in paediatric patients in Child–Pugh class A - with dose adjustment

For these simulations, all simulated paediatric patients were considered to have chronic liver disease according to Child-Pugh class A. The adult reference was maintained as before. Figure 6 and Table 9 show the simulated PK metrics by WT bins. It shows that the adjusted WT-based dosing regimen (for hepatic impairment) results in less or similar variability in children than/as observed in adults. The 90% CI in adults shows a wider range of exposures, compared to children, with more extreme values for adults, at the upper or lower end. However, some children (with intermediate weight) have slightly higher Cmax,ss than adults with low weight. Compared to the overall geometric mean exposure in adults without hepatic impairment, the four dose groups in this scenario are predicted to differ between -10% and +49% for AUCτ,ss (and Cav,ss), between +13% and +76% for Cmax,ss, and between -38% and +17% for Ctrough,ss.

Figure 6: Predicted nintedanib $C_{av,ss}$, $AUC_{\tau,ss}$, $C_{trough,ss}$ and $C_{max,ss}$ versus WT bins and stratified by age group, for the PK simulation data set with Child-Pugh class A and dose adjustment. The blue line is the geometric mean and the blue area spans from the 5th to the 95th percentile, for each WT bin. As reference, the gray area spans from the 5th to the 95th percentile across all adults (without hepatic impairment) and the horizontal line indicates the adult geometric mean ($C_{av,ss}$ (red): 26 nM, $AUC_{\tau,ss}$ (orange): 316nM·h, $C_{trough,ss}$ (green): 20 nM, and $C_{max,ss}$ (purple):33 nM). An orange rug (brush border) along the x-axis indicates the lowest WT in each WT bin.

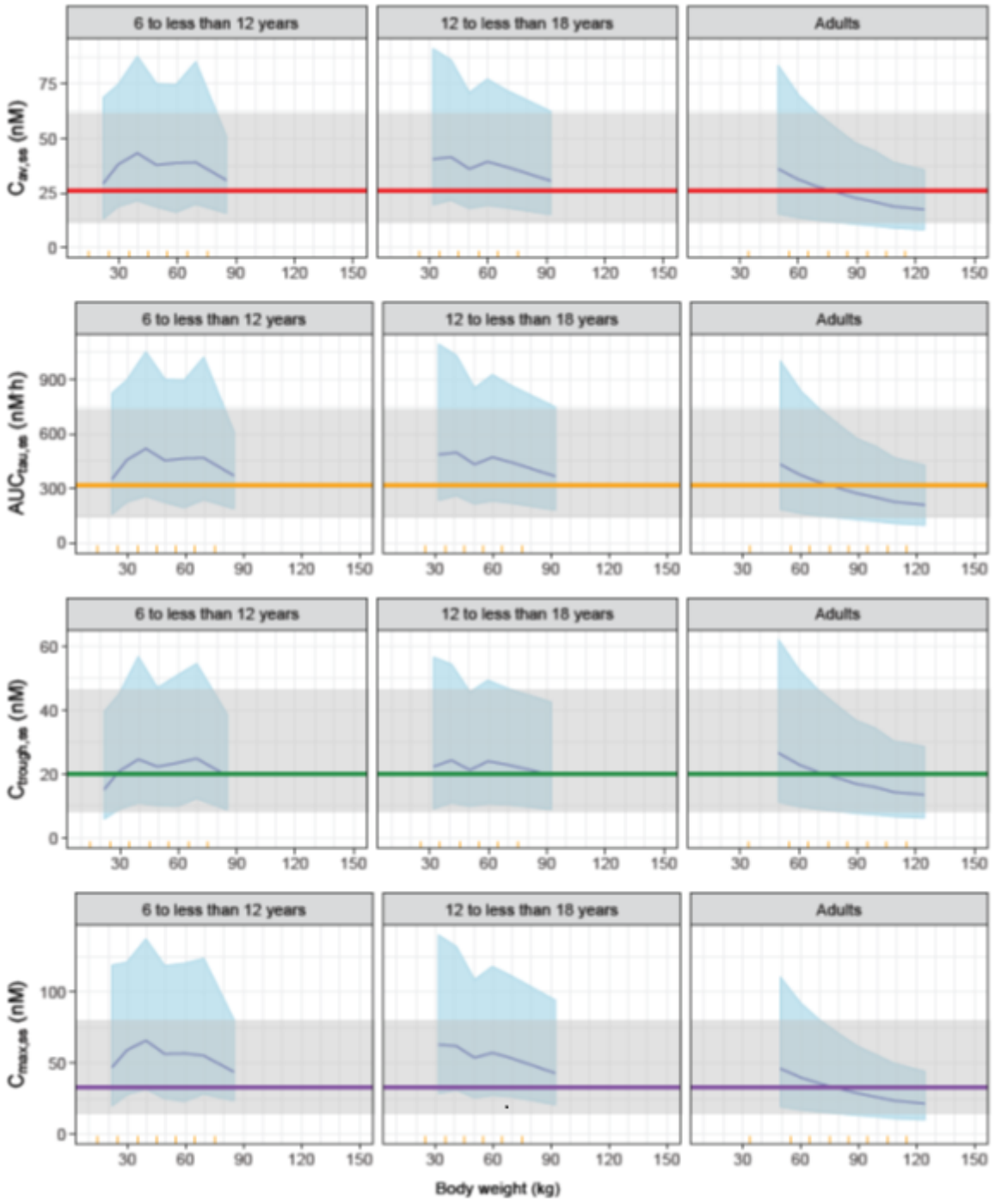


Table 9: Predicted geometric mean (5th and 95th percentiles) for nintedanib PK parameters by WT band for the paediatric subjects in the PK simulation data set with Child-Pugh class A and dose adjustment.

WT/Regimen	Age[a] (years)	WT[b] (kg)	Fem.[c] (%)	Frac.[d] (%)	$AUC_{\tau,ss}$[e] (nM·h)*	$C_{av,ss}$[e] (nM)*	$C_{max,ss}$[e] (nM)*	$C_{trough,ss}$[e] (nM)*	$t_{max,ss}$[e] (h)	CL/F[e] (L/h)	V/F[e] (L)
13.5 to <23.0 kg											
25 mg BID	7.00	20.6	51.7	7.15	284 (145, 556)	23.7 (12.1, 46.4)	37.9 (18.2, 80.8)	12.3 (5.32, 26.0)	1.87 (0.963, 3.84)	345 (303, 372)	2940 (2470, 3260)
23.0 to <33.5 kg											
50 mg BID	8.54	27.9	46.1	21.2	450 (223, 885)	37.5 (18.6, 73.7)	58.6 (27.3, 121)	20.5 (8.96, 44.4)	1.85 (0.948, 3.92)	432 (381, 489)	3970 (3360, 4680)
33.5 to <57.5 kg											
75 mg BID	12.3	45.8	54.5	40.0	471 (231, 981)	39.3 (19.2, 81.8)	58.9 (27.3, 126)	23.0 (10.4, 50.9)	1.87 (0.950, 3.98)	622 (509, 733)	6460 (4940, 8040)
≥57.5 kg											
100 mg BID	14.9	74.8	43.5	31.6	432 (208, 888)	36.0 (17.3, 74.0)	51.6 (23.8, 113)	22.7 (10.1, 47.7)	1.88 (0.956, 4.03)	893 (754, 1200)	10500 (8340, 15600)

[a] Mean age for the subjects in each WT band in the PK simulation data set
[b] Mean WT for the subjects in each WT band in the PK simulation data set
[c] Fraction female among the subjects in each WT band in the PK simulation data set
[d] Fraction of subjects for each WT band, in relation to the whole pediatric population used in the simulations
[e] Summarized as geometric mean (5th, 95th percentiles). For the two disposition parameters (CL/F and V/F) values shown are in relation to the population typical F (without hepatic impairment), so that between-subject variability in F is not included.
* Molecular weight of nintedanib: 540 g/mol.

3.3.1.2 Pharmacodynamics

Population PKPD analysis of nintedanib in paediatric patients with fibrosing Interstitial Lung Disease

The aim of this analysis was to develop exposure-response models to describe the relationship between nintedanib PK and annual rate of decline in %predicted forced vital capacity (FVC) and FVC Z-score in children and adolescent patients 6 to less than 18 years of age with documented clinically significant fibrosing ILD.

The analyses are based on paediatric data from the Phase III study InPedILD (1199-0337) and its open-label extension study InPedILD-ON (1199-0378) up to 31 May 2023. Previous exposure-response analyses for efficacy, based on data from adult patients with idiopathic pulmonary fibrosis (IPF), systemic sclerosis associated ILD (SSc-ILD) and progressive fibrosing ILDs (PF-ILD) other than IPF were used as prior information to support the paediatric modelling.

With the limited number of paediatric patients possible to recruit and the ethical issues of exposing paediatric patients to placebo treatment over longer time periods, the intention was not to generate independent evidence for efficacy in the paediatric population, but rather to investigate whether the emerging data from InPedILD are consistent with the adult prior.

The PK/PD analyses included data from 48 paediatric patients for with 465 FVC measurements. Subject characteristics for the paediatric patients in the PKPD analysis data set are presented by arm and age group in Table 10 and Table 11.

Table 10: Baseline characteristics for the patients in the PKPD analysis data set, by arm and age group: continuous covariates

	[6-12) yo - Placebo N=4	[6-12) yo - Active N=13	[12-18) yo - Placebo N=9	[12-18) yo - Active N=22	Overall N=48
Body weight (kg)					
Mean (SD)	26.6 (9.45)	25.4 (10.5)	52.7 (20.5)	48.4 (12.7)	41.2 (17.8)
Median (min, max)	27.8 (15.2, 35.7)	20.6 (15.2, 50.0)	55.7 (22.3, 75.4)	45.8 (32.0, 94.9)	41.1 (15.2, 94.9)
Height (cm)					
Mean (SD)	136 (18.5)	127 (12.9)	154 (12.5)	157 (10.8)	147 (17.9)
Median (min, max)	136 (116, 155)	123 (109, 149)	152 (131, 171)	156 (136, 185)	152 (109, 185)
Age (y)					
Mean (SD)	9.90 (1.75)	9.11 (1.82)	15.0 (1.48)	15.0 (1.95)	13.0 (3.30)
Median (min, max)	10.4 (7.41, 11.5)	9.11 (6.23, 11.9)	14.4 (13.0, 17.4)	15.4 (12.3, 17.7)	13.2 (6.23, 17.7)
Absolute FVC (mL)					
Mean (SD)	1450 (617)	953 (447)	2150 (1080)	2010 (967)	1700 (967)
Median (min, max)	1640 (574, 1940)	823 (419, 1790)	2420 (548, 3480)	2030 (736, 4220)	1450 (419, 4220)
Predicted FVC (%)					
Mean (SD)	64.7 (17.2)	52.9 (20.6)	62.1 (25.6)	59.0 (21.9)	58.4 (21.6)
Median (min, max)	69.0 (40.3, 80.5)	56.2 (28.1, 98.6)	57.6 (25.3, 103)	61.9 (22.2, 92.4)	58.7 (22.2, 103)
FVC Z-score					
Mean (SD)	-2.97 (1.35)	-3.99 (1.73)	-3.27 (2.18)	-3.53 (1.93)	-3.56 (1.86)
Median (min, max)	-2.67 (-4.86, -1.69)	-3.76 (-6.00, -0.112)	-3.70 (-6.32, 0.232)	-3.20 (-7.12, -0.640)	-3.52 (-7.12, 0.232)

[6-12) yo = 6 to less than 12 years, [12-18) yo = 12 to less than 18 years, Active = nintedanib arm.
Baseline characteristics, arm and age groups are computed at the very first visit (Section 4.1).

Table 11: Baseline characteristics for the patients in the PKPD analysis data set, by arm and age group: categorical covariates

	[6-12) yo - Placebo N=4	[6-12) yo - Active N=13	[12-18) yo - Placebo N=9	[12-18) yo - Active N=22	Overall N=48
Sex					
Male	2 (50%)	8 (62%)	3 (33%)	7 (32%)	20 (42%)
Female	2 (50%)	5 (38%)	6 (67%)	15 (68%)	28 (58%)
ILD diagnosis[a]					
Pediatric autoimmune ILD	2 (50%)	1 (7.7%)	2 (22%)	9 (41%)	14 (29%)
Surfactant Protein Deficiency	1 (25%)	4 (31%)	4 (44%)	5 (23%)	14 (29%)
Other fibrosing ILD	1 (25%)	5 (38%)	2 (22%)	3 (14%)	11 (23%)
Toxic/Radiation/Drug Induced Pneumonitis	0 (0%)	2 (15%)	1 (11%)	3 (14%)	6 (12%)
Chronic hypersensitivity pneumonia	0 (0%)	1 (7.7%)	0 (0%)	1 (4.5%)	2 (4.2%)
Post HSCT Fibrosis	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)	1 (2.1%)
Systemic sclerosis[a]					
SSc-ILD	2 (50%)	0 (0%)	1 (11%)	4 (18%)	7 (15%)
Non-SSc-ILD	2 (50%)	13 (100%)	8 (89%)	18 (82%)	41 (85%)

[a] All SSc-ILD patients were included in Ped. Autoimmune ILD
[6-12) yo = 6 to less than 12 years, [12-18) yo = 12 to less than 18 years, Active = nintedanib arm.
Numbers represent the number of patients in each category and the corresponding percentage in relation to the total number of patients as specified in the column header.
Baseline characteristics, arm and age groups are computed at the very first visit (Section 4.1).

The PKPD external-evaluation and starting models for %predicted FVC and FVC Z-score consisted of a linear placebo model, to describe natural disease progression, and a maximum effect (Emax) model to describe the relationship between nintedanib Ctrough,ss and response, for both endpoints. IIV terms were included on the parameters describing the baseline and placebo slope (annual rate of decline) and on the magnitude of RUV. No covariates from the adult %predicted FVC and FVC Z-score models were retained. All fixed and random effects (population) parameters of the pre-specified models were subsequently updated. The placebo slope, Emax, concentration at half maximum effect (EC50) and IIV on placebo slope were supported with the adult prior. The baseline, IIV on baseline, IIV on RUV (where present) and RUV were estimated without support of the prior.

Typical population predictions of change from baseline in %predicted FVC and FVC Z-score for subjects on the InPedILD starting doses (and/or updated dosing regimen, if required) and placebo including associated parameter uncertainty, were generated using the final %predicted FVC and FVC Z-score

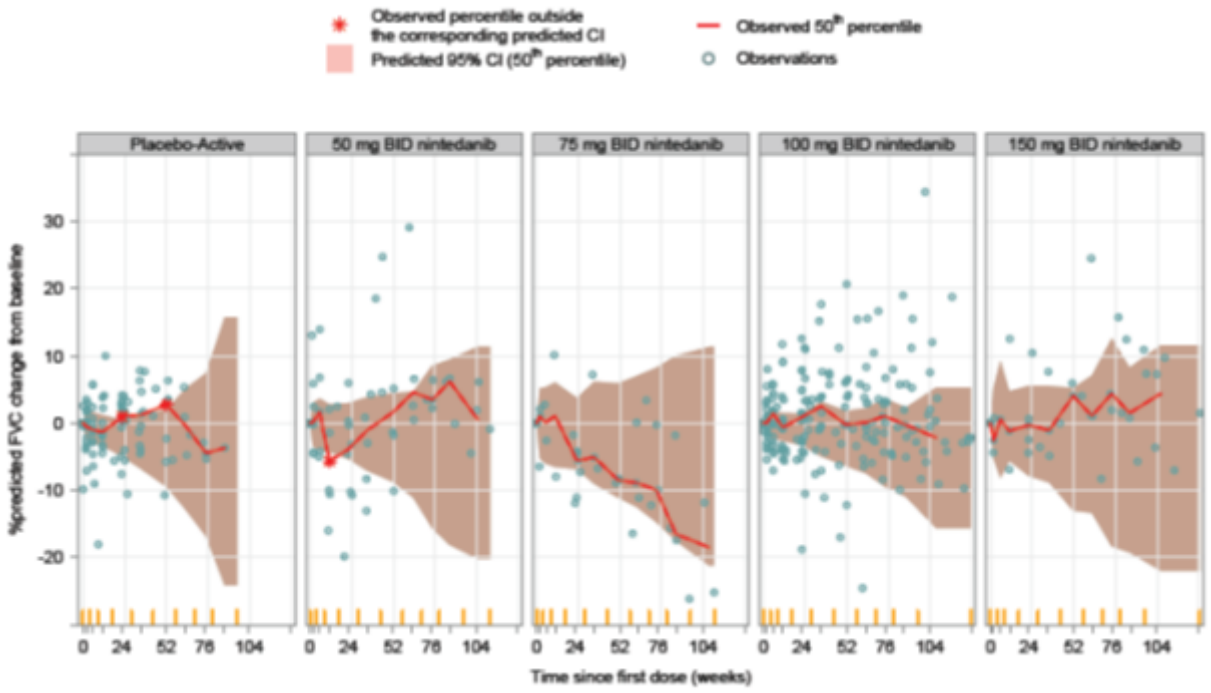
models and the median Ctrough,ss per age and dose group. In addition, the change from baseline in %predicted FVC and FVC Z-score for subjects on the InPedILD starting doses and placebo including IIV was simulated using the individually simulated Ctrough,ss.

Results

%predicted FVC

An external evaluation of the adult model with population parameters fixed to previously reported values was performed on the %predicted FVC data from InPedILD and InPedILD-ON.

Figure 7: External VPC of % predicted FVC observations in InPedILD and InPedILD-ON, stratified by dose at start of each study, using the external evaluation % predicted FVC model. % predicted FVC observations are displayed as delta change from baseline versus time since first dose. The observed data are indicated by open circles. The solid red line represents the median of the observations; the red stars indicate that the percentile is outside the predicated CI and the shaded red areas represents the 95% confidence interval of the median predicted by the model. The orange brush border along the x-axis indicates the bins across time.



As a first step in the model development, the pre-specified model was re-estimated on the %predicted FVC analysis data set with population priors based on the adult analysis. SCM identified a difference in Slope in children (less than 12 years old) versus adolescent and adult patients. Thus, a covariate effect describing a difference in Slope in children (less than 12 years old) versus adolescent and adult patients was included in the final model.

The final model for %predicted FVC consisted of a linear placebo model, with a covariate effect describing the change in annual rate of decline for children aged 6 to less than 12 years, and an Emax model to describe the relationship between nintedanib Ctrough,ss and %predicted FVC response. IIV terms were supported on RUV, Baseline and Slope and the RUV was described by an additive error model. Slope, Emax, EC50 and IIV on adult slope were supported by the adult prior. Baseline, RUV and IIV on Baseline and IIV on RUV were estimated independent of the adult prior. With the covariate describing the difference in slope for children from 6 to less than 12 years old, the slope for children

was released from the adult prior, and thereby estimated independently, as well. The parameter estimates of the final %predicted FVC model are presented in Table 12, in comparison to the base model. The EC50 estimated in the final model was 8.06 nM (4.35 ng/mL) and the Emax was an improvement (over placebo) in the rate of decline of 4.22%/year. The estimates of Emax and EC50 were similar to the results in adults. A VPC plot for %predicted FVC, for the final %predicted FVC PKPD model is presented in Figure 8.

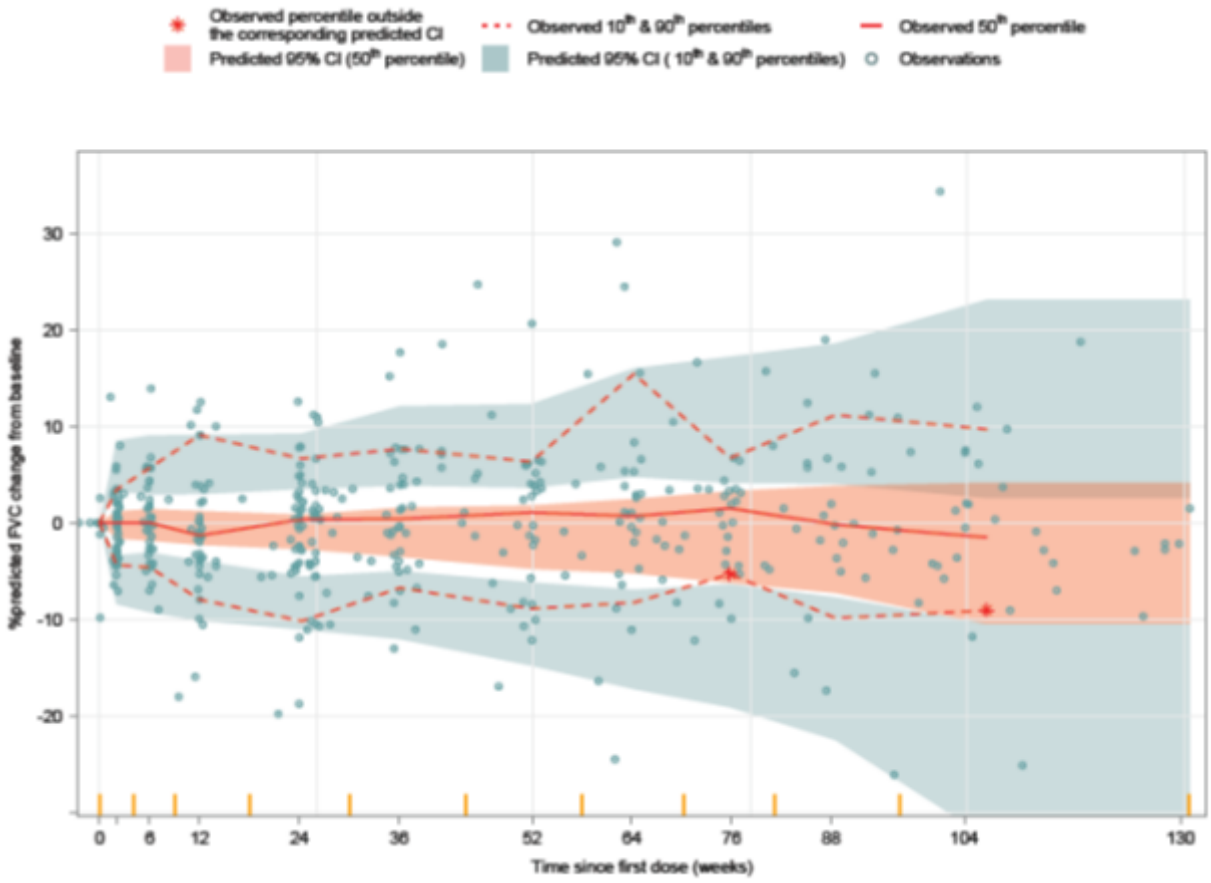
Table 12: Parameter estimates of the final %predicted FVC model, compared to the base %predicted FVC model.

		Final model			Base model		
Run		203			202		
OFV		6665.86			6670.36		
Condition number		10.76			9.95		
		Final model			**Base model**		
	Unit	**Value**	**RSE (%)**	**SHR (%)**	**Value**	**RSE (%)**	**SHR (%)**
Baseline	%	54.1	5.98		54.2	5.93	
Slope*	%/year	-4.74	4.24		-4.73	4.25	
E_{max}*	%/year	4.22	12.2		4.25	11.7	
EC_{50}*	nM	8.06	27.9		7.98	27.0	
Change in Slope for children[a]	%/year	3.96	45.6				
IIV Baseline	CV	0.413	10.3	0	0.412	10.3	0
IIV Slope*	SD, %/year	5.58	2.16	10.3	5.59	2.16	10.3
IIV RUV	CV	0.395	14.5	7.92	0.402	14.3	7.59
Add. RUV	%	3.10	7.27	2.77	3.10	7.35	2.71

* supported by adult priors.

[a] Translating into a Slope of -0.781 %predicted FVC/year for a child aged 6 to less than 12 years.

Figure 8: VPC of %predicted FVC change from baseline versus time since first dose, for the final population %predicted FVC model based on the %predicted analysis data set. The observed data (presented as delta change from baseline) are indicated by open circles. The solid and dashed red lines represent the median, 10th and 90th percentiles of the observations; the red stars indicate that the percentile is outside the corresponding predicted CI and the shaded red and blue areas represent the 95% CI of the median, 10th and 90th percentiles predicted by the model (n=500 replicates). The orange brush along the x-axis indicates the bins across time.



Forest plots for the model parameters that are impacted by covariate effects are presented in Figure 9. The Slope panel illustrates the impact on the annual change from baseline (disease-progression rate). As the typical adult patient has a negative slope (deterioration over time), a relative parameter value <0 represents a positive slope (increase over time), in the typical paediatric patient.

Figure 9: Forest plots based on the final %predicted FVC model for the model parameter that is impacted by covariates. The impact of the covariate(s) is evaluated at the values shown on the y-axis (i.e., the 2.5 percentile, median and 97.5 percentile of the distribution of age at baseline in the %predicted FVC analysis data set) and are displayed on a relative scale of the x-axis. The reference set of covariate values, indicated by the vertical solid grey line, is provided in the plot header. The dashed vertical lines indicate the region of 0.8-1.25 relative to the reference set of covariates. The closed symbols represent the median parameter estimates and the whiskers represent the 95% CI based on 2000 SIR replicates. The median and CI limits are provided numerically to the right of the panel.

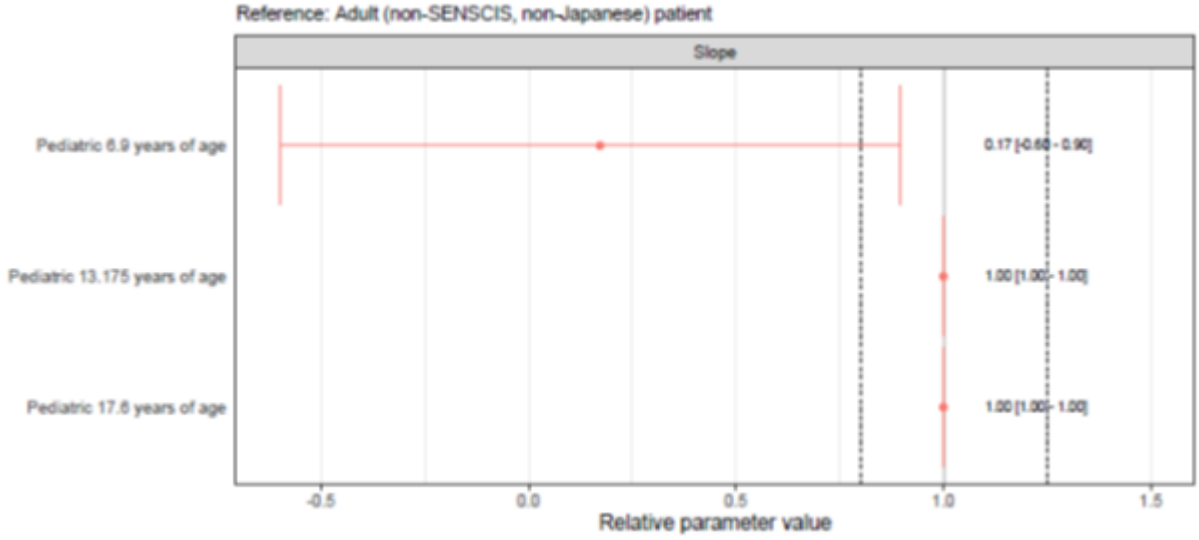
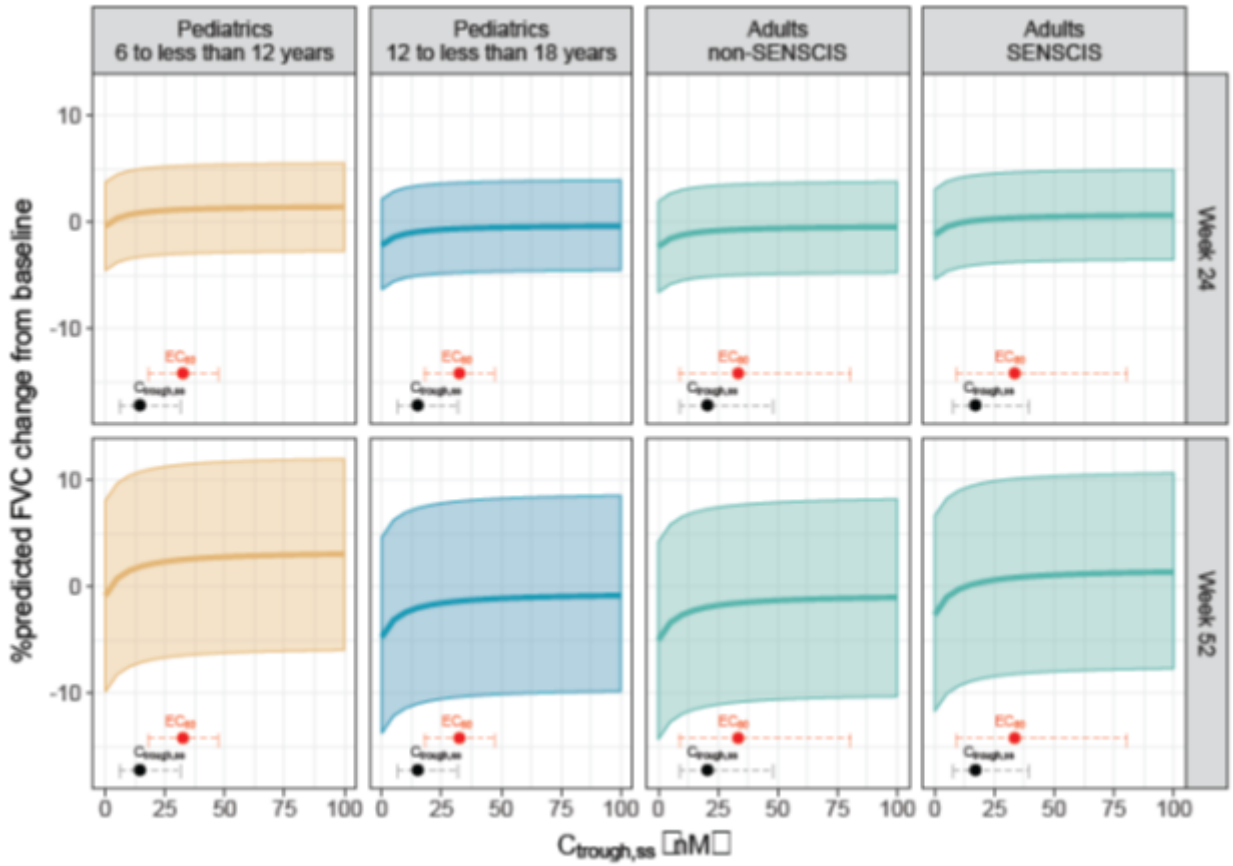


Figure 10 shows the simulated change from baseline in %predicted FVC at week 24 and week 52 after start of treatment versus Ctrough,ss. The typical exposure is above the estimated EC50 values and therefore approaching the plateau of the exposure-response relationship.

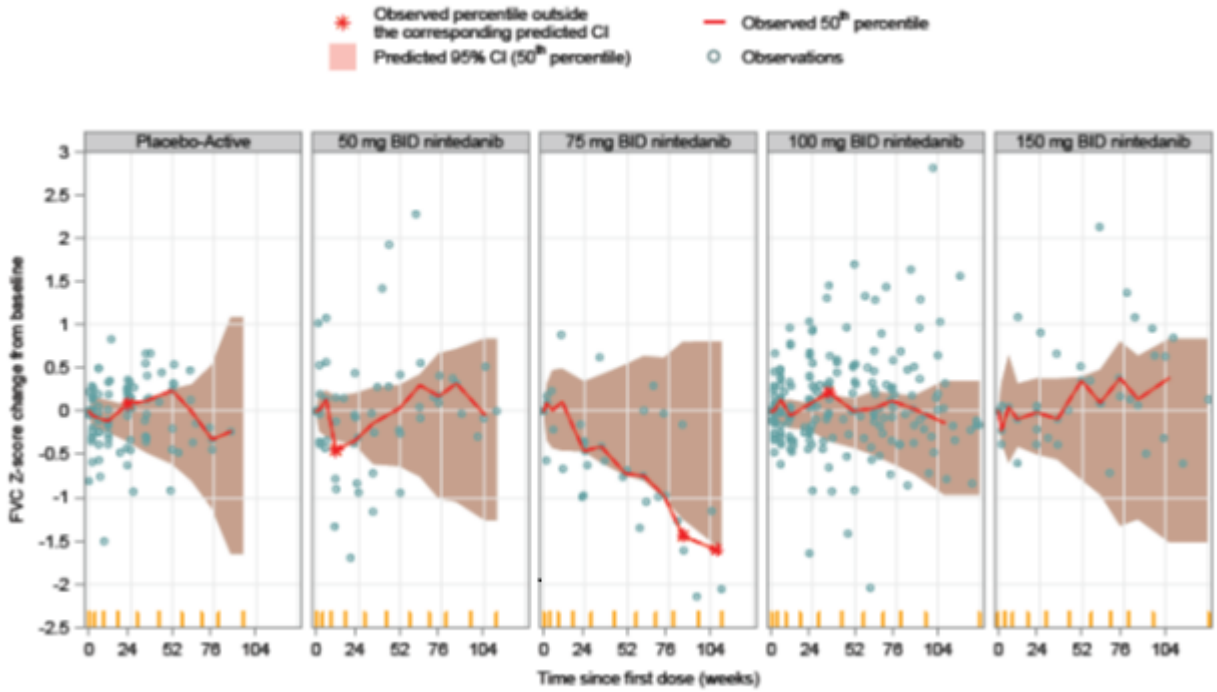
Figure 10: Individual predictions of %predicted FVC change from baseline (presented as delta change from baseline) versus $C_{trough,ss}$ for the final %predicted FVC model, stratified by age group and by study for adults. The solid lines represent the mean &predicted FVC change from baseline at 24 and 52 weeks versus $C_{trough,ss}$ and the shaded areas are the 90% prediction intervals, representing variability between subjects. The black filled circle indicates the median $C_{trough,ss}$ in the presented group, and the dashed gray line indicates the 5^{th} and 95^{th} percentiles of Ctrough,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, which represents uncertainty in the population parameters (not variability between patients).



FVC Z-score

An external evaluation of the adult model with population parameters fixed to previously reported values was performed on the FVC Z-score data from InPedILD and InPedILD-ON.

Figure 11: External VPC of FVC Z-score observations in InPedILD and InPedILD-ON, stratified by dose at start of each study, using the external evaluation FVC Z-score model. FVC Z-score observations are displayed as delta changes from baseline versus time since first dose. The observed data are indicated by open circles. The solid red line represents the median of the observations; the red stars indicate that the percentile is outside the predicated CI and the shaded red areas represent the 95% confidence interval of the median predicted by the model. The orange brush border along the x-axis indicates the bins across time.



As a first step in the model development, the pre-specified model was re-estimated on the FVC Z-score analysis data set with population priors based on the adult analysis. SCM identified a difference in the magnitude of IIV on Slope, where younger paediatric patients had a higher magnitude of IIV, than adults. Thus, a covariate describing the effect of paediatric age on IIV slope was included in the final model.

The final model for FVC Z-score consisted of a linear placebo model, with a covariate effect describing the change in paediatric annual rate of decline, and an Emax model to describe the relationship between nintedanib Ctrough,ss and FVC Z-score response. IIV terms were supported on RUV, Baseline and Slope and the RUV was described by an additive model. Slope, Emax, EC50 and IIV on Slope were supported by the adult prior. Baseline, RUV and IIV on Baseline and RUV were estimated independent of the adult prior. The parameter estimates of the final FVC Z-score model are presented in Table 13, in comparison to the base model. The EC50 estimated in the final model was 7.97 nM (4.30 ng/mL) and the Emax was an improvement (over placebo) in the rate of decline of 0.295 Z-score/year. The estimates of Emax and EC50 were similar to the results in adults. A VPC plot for FVC Z-score, for the final FVC Z-score PKPD model is presented in Table 13.

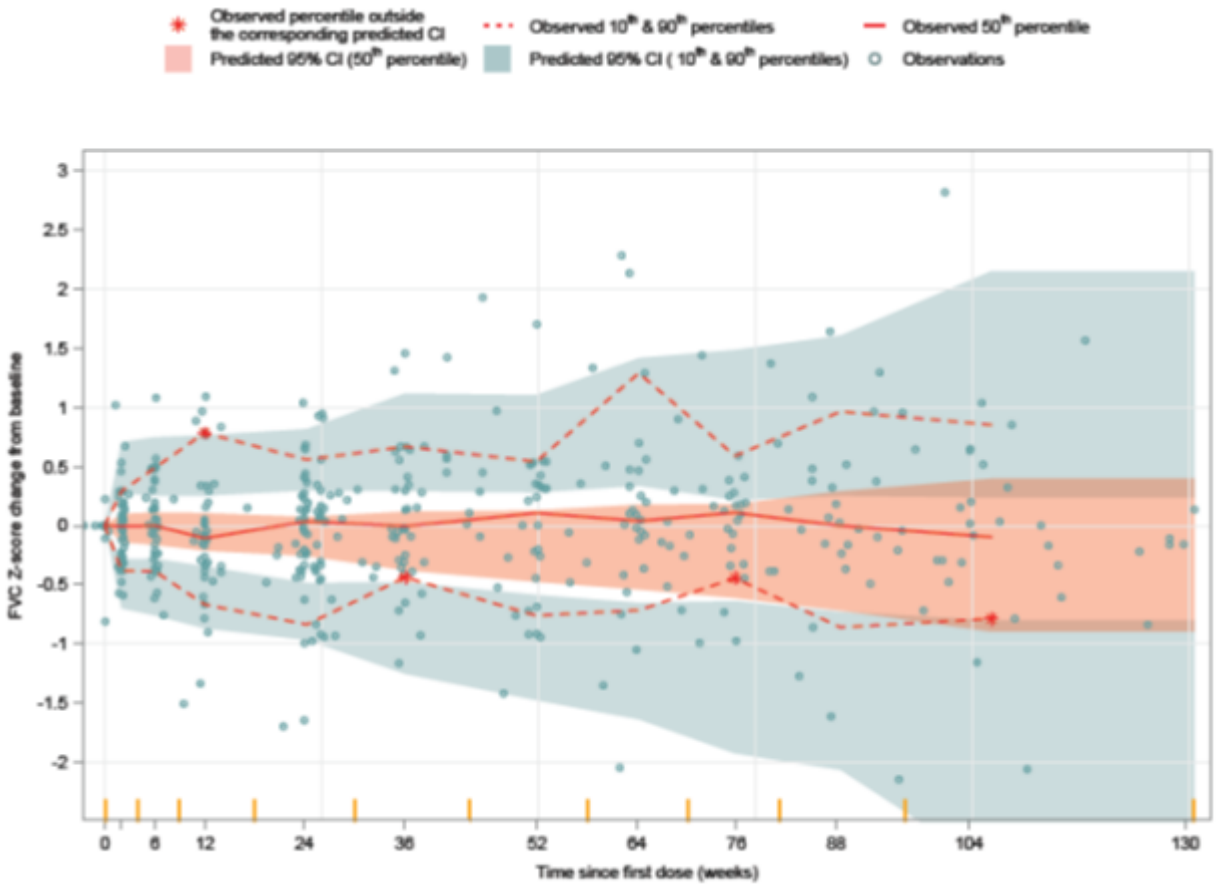
Table 13: Parameter estimates of the final FVC Z-score model, compared to the base FVC Z-score model.

	Final model	Base model
Run	102	101
OFV	-1250.44	-1244.55
Condition number	42.25	103.38

		Final model			Base model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
Baseline	Z-score	-3.56	7.64		-3.54	7.65	
Slope*	Z-score/year	-0.308	4.58		-0.308	5.03	
E_{max}*	Z-score/year	0.295	23.3		0.279	35.4	
EC_{50}*	nM	7.97	77.8		6.23	157	
Pediatric age on IIV Slope	rel. change per yoa	-0.0860	34.5				
IIV Baseline	SD, Z-score	1.89	10.3	0	1.87	10.3	0
IIV Slope*	SD, Z-score/year	0.379	2.19	14.7	0.381	2.19	1.63
IIV RUV	CV	0.368	15.0	9.76	0.399	14.2	7.85
Add. RUV	Z-score	0.261	6.91	3.07	0.263	7.32	2.71

* supported by adult priors.

Figure 12: VPC of FVC Z-score change from baseline versus time since first dose, for the final population FVC Z-score model based on the FVC Z-score analysis data set. The observed data (presented as delta change from baseline) are indicated by open circles. The solid and dashed red lines represent the median, 10th and 90th percentiles of the observations; the red stars indicate that the percentile is outside the corresponding predicted CI and the shaded red and blue areas represent the 95% CI of the median, 10th and 90th percentiles predicted by the model (n=500 replicates). The orange brush border along the x-axis indicates the bins across time.



Forest plots for the model parameters that are impacted by covariate effect(s) are presented in Figure 13.

Figure 13: Forest plots based on the final FVC Z-score model for the model parameters(s) that are impacted by covariates. The impact of the covariate(s) is evaluated at the values shown on the y-axis (i.e., the 2.5 percentile, median and 97.5 percentile of the distribution of age at baseline in the FVC Z-score analysis data set) and are displayed on a relative scale on the x-axis. The reference set of covariate values, indicated by the vertical solid grey line, is provided in the plot header. The dashed vertical lines indicate the region of 0.8-1.25 relative to the reference set of covariates. The closed symbols represent the median parameter estimates and the whiskers represent the 95% CI based on 2000 SIR replicates. The median and CI limits are provided numerically to the right of the panel.

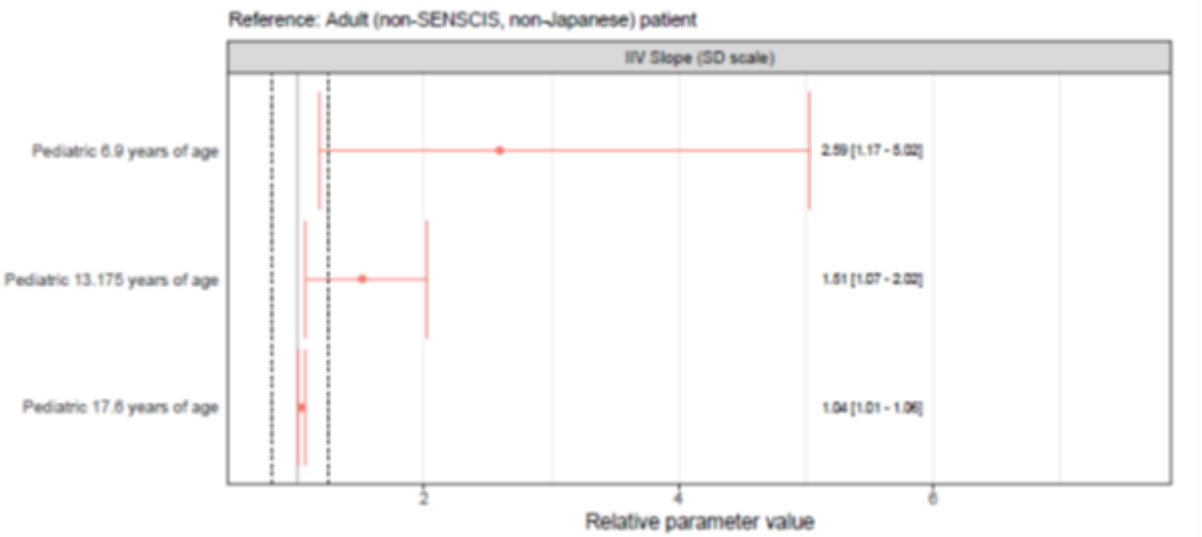
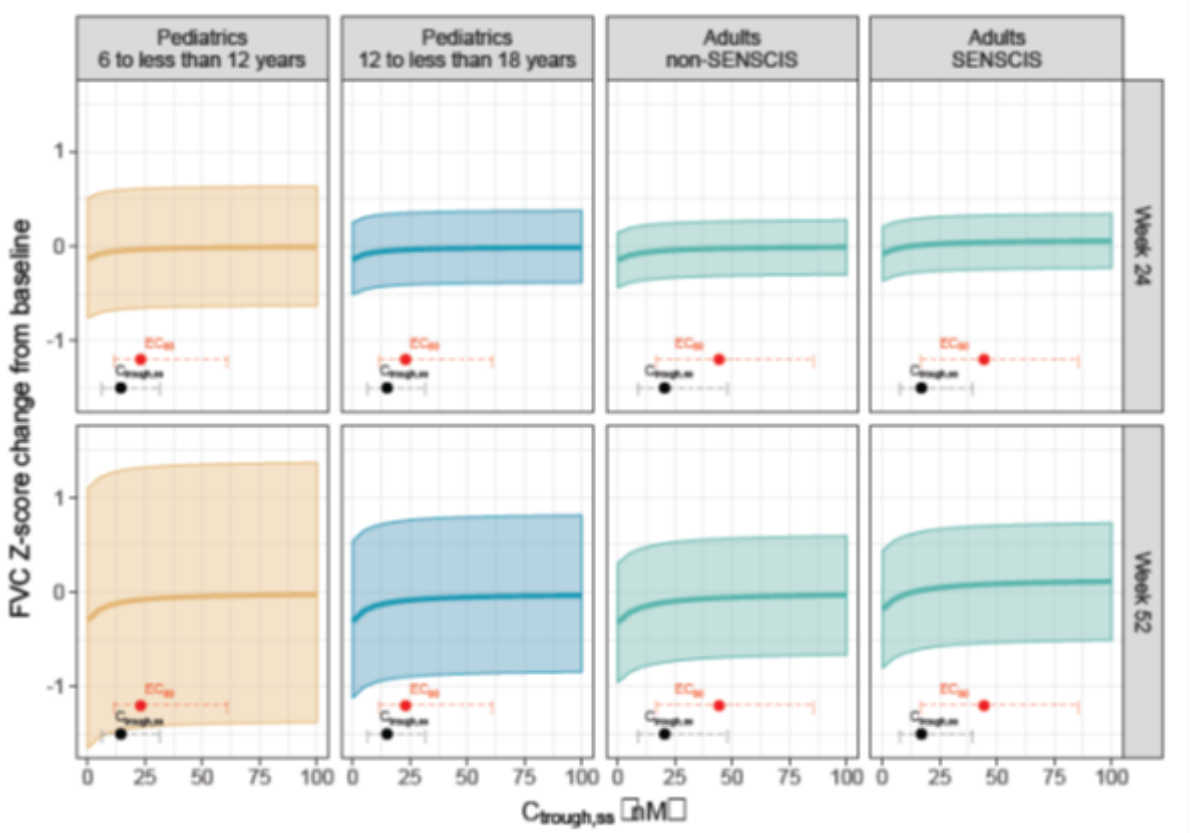


Figure 14 shows the simulated change from baseline in FVC Z-score at week 24 and week 52 after start of treatment versus Ctrough,ss. The typical exposure is above the estimated EC50 values and therefore approaching the plateau of the exposure-response relationship.

Figure 14: Individual predictions of FVC Z-score change from baseline (presented as delta change from baseline) versus $C_{trough,ss}$ for the final FVC Z-score model, stratified by age group and by study for adults. The solid lines represent the mean FVC Z-score change from baseline at 24 and 52 weeks versus $C_{trough,ss}$ and the shaded areas are the 90 % prediction intervals, representing variability between subjects. The black filled circle indicates the median $C_{trough,ss}$ in the presented group, and the dashed gray line indicates the 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, which represents uncertainty in the population parameters (not variability between patients).



Exposure-safety correlation for selected safety markers

The relationship between exposure and liver enzyme (ALT and AST) elevations as well as the occurrence of diarrhoea in InPedILD and InPedILD-ON was assessed descriptively. Individual predicted nintedanib Ctrough,ss values were summarised by liver enzyme elevation (ALT or AST < 3x ULN versus ≥ 3x ULN) and diarrhoea events ('yes' versus 'no'). In addition, predicted nintedanib predicted Cmax,ss values were summarised by liver enzyme elevation and diarrhoea events.

Based on the pooled data from 1199-0337 and 1199-0378 (up to 31-May-2023), two patients had on-treatment liver enzyme elevations (defined as AST or ALT ≥ 3x ULN) based on central laboratory assessment. The Ctrough,ss in these 2 patients were in the range of the exposures observed in 45 paediatric patients without liver enzyme elevations (Figure 15). Figure 16 presents nintedanib Cmax,ss in patients with and without liver enzyme elevations.

In addition, three patients (2 in 1199-0337 and one in 1199-0378; all in the 12 to < 18 years of age group) were reported with liver injury based on elevated ALT and AST values as per local laboratory assessment (ALT > 3x ULN, AST > 2.5x ULN). The exposure of one of those patients was higher than those observed for the other paediatric patients: the $AUC_{T,ss}$ in this patient was 515 ng·h/mL at Week

26 (gMean for patients aged 12 to <18 years: 167 h·ng/mL). Cmax,ss in this patient was 99.5 ng/mL at Week 26 (gMean for patients aged 12 to <18 years: 33.0 ng/mL). Exposures of other two patients were within the range of exposures observed for the other patients.

Figure 15: Boxplots of predicted $C_{trough,ss}$ values of nintedanib by liver enzyme elevation (ALT/AST <3x versus **≥3x** ULN as per central laboratory) for adults and the paediatric population in trials 1199-0337 and 1199-0378 pooled

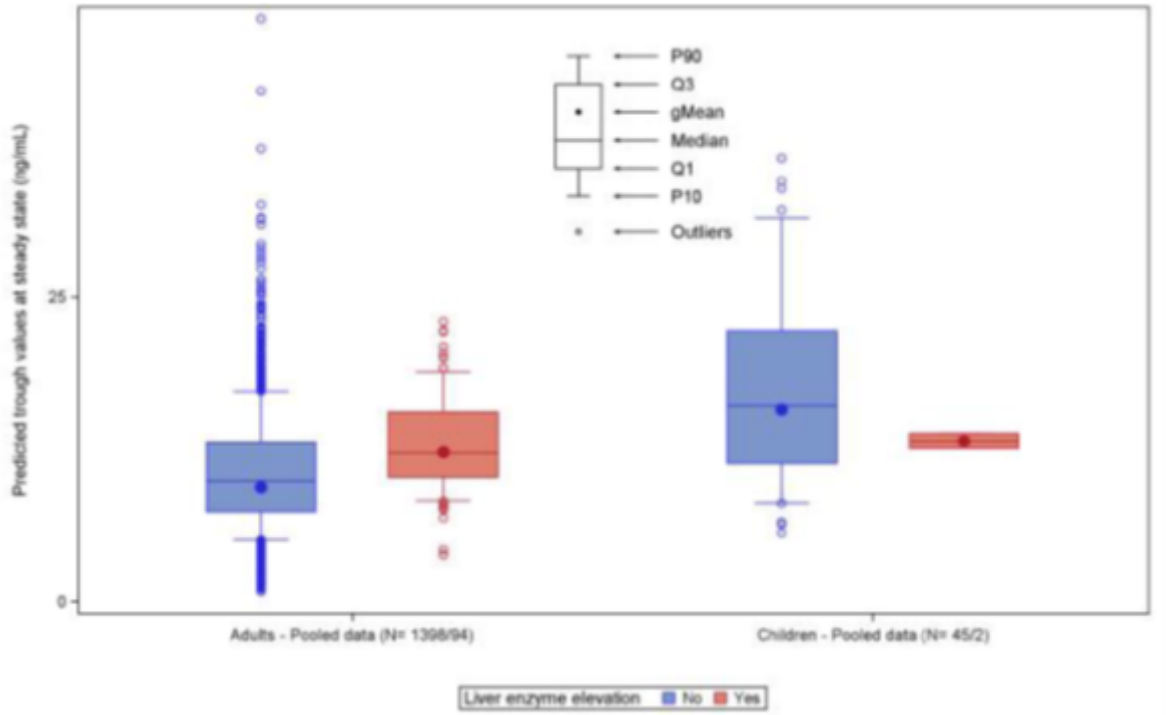


Figure 16: Boxplot of individual and gMean predicted $C_{max,ss}$ of nintedanib by liver enzyme elevation event for the adult and paediatric patient population.

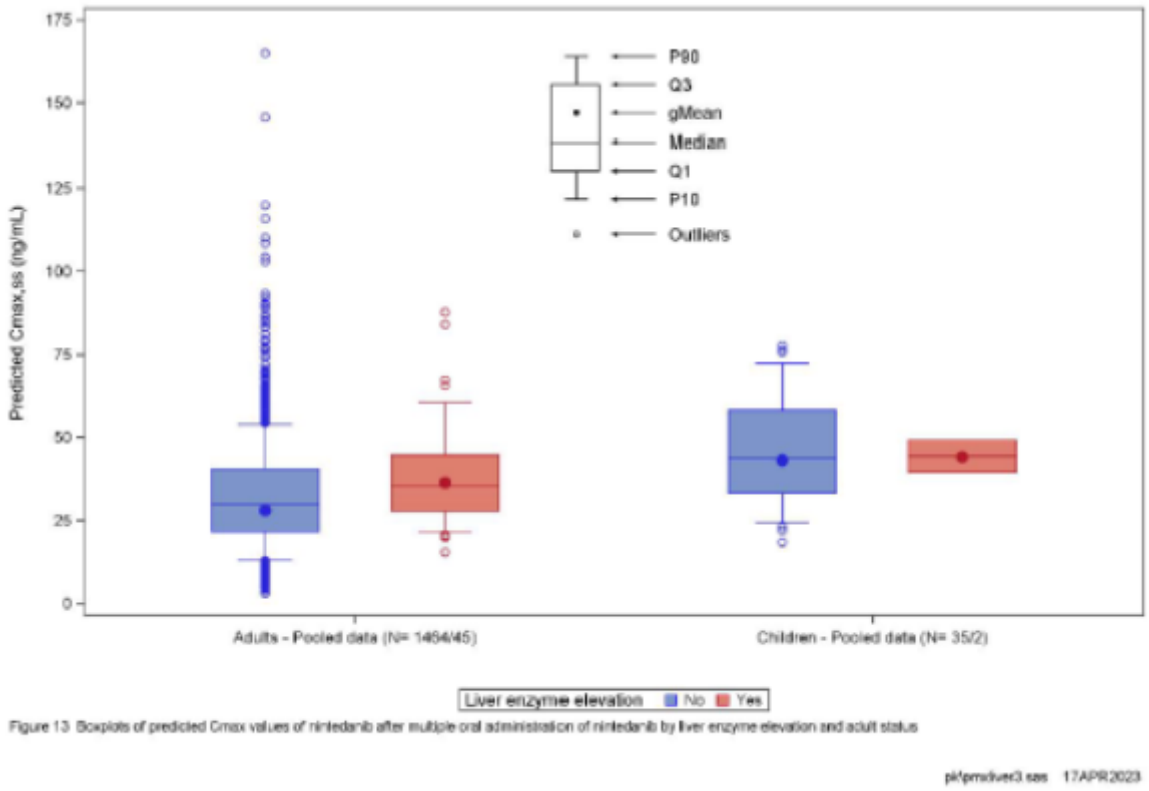


Figure 13 Boxplots of predicted Cmax values of nintedanib after multiple oral administration of nintedanib by liver enzyme elevation and adult status

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Diarrhoea was reported for 22 out of 47 paediatric patients while receiving nintedanib in the double-blind or open-label period of InPedILD and InPedILD-ON. Nintedanib Ctrough,ss and Cmax,ss concentrations comparing patients with and without diarrhoea event are shown in Figure 17 and Figure 18 respectively. These show no apparent difference in exposure between paediatric patients with and without diarrhoea events.

Figure 17: Boxplot of individual and geometric mean predicted $C_{trough,ss}$ values of nintedanib by diarrhea of event for the adult population and the paediatric population in trials 1199-0337 and 1199-0378 pooled.

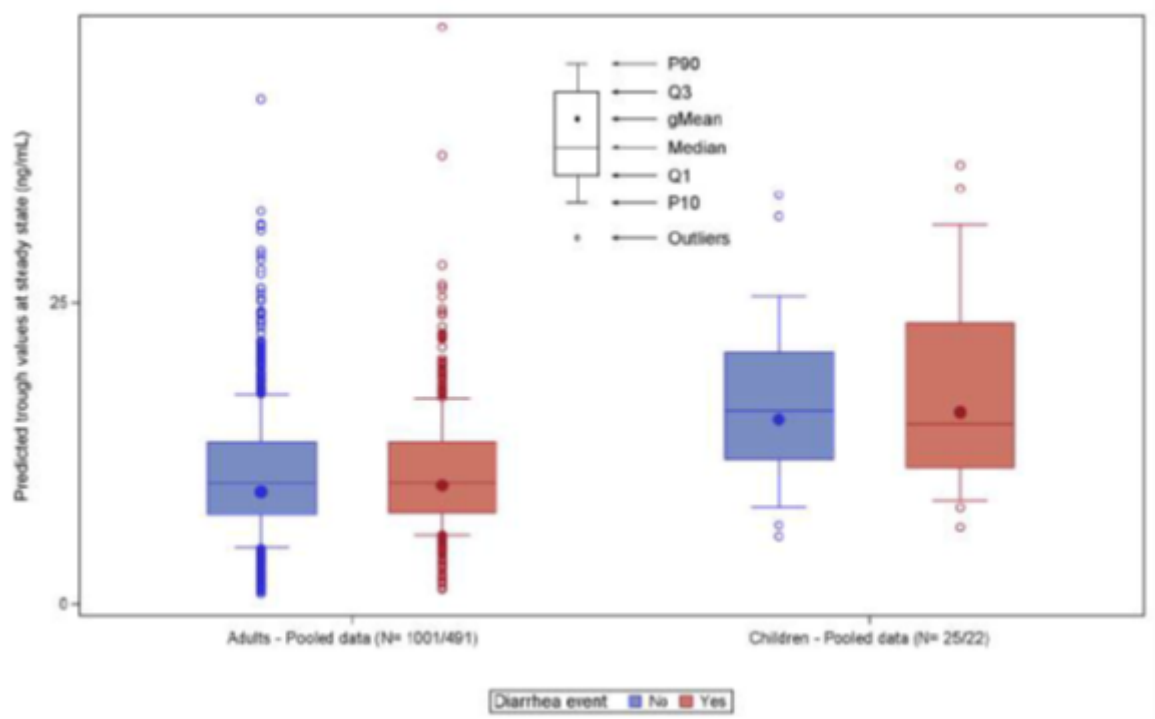

Figure 18: Boxplot of individual and gMean predicted $C_{max,ss}$ of nintedanib by diarrhoea event for the adult and paediatric patient population.

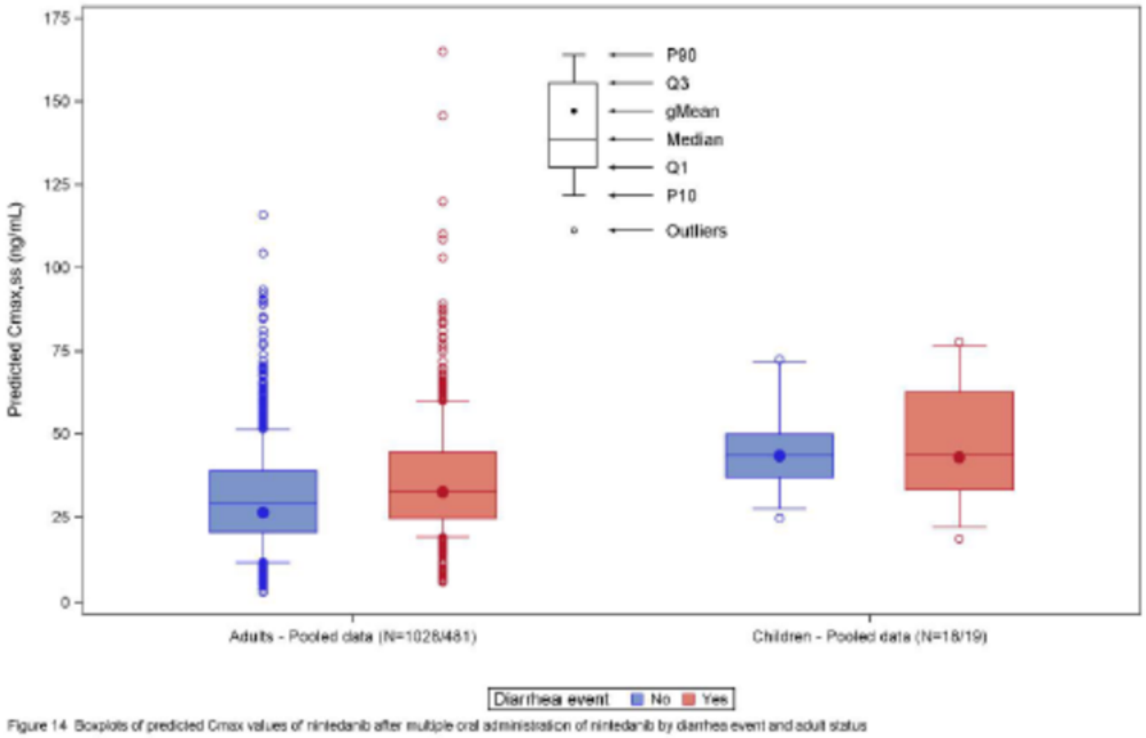

Figure 14 Boxplots of predicted Cmax values of nintedanib after multiple oral administration of nintedanib by diarrhea event and adult status

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Dose justification

Nintedanib was administered based on body weight in InPedILD and InPedILD-ON, with the aim to match the exposures observed in adult patients considered to be efficacious (following administration of nintedanib 150 mg BID). The weight bins and dose levels were selected using population PK modelling with allometric scaling of clearance and volume. The PK parameter to be matched was

$AUC_{\tau,ss}$. The weight-bins and selected doses are given in Table 14.

Table 14: Dose assignment and dose reduction possibility based on body weight bin according to ICH E11

Body weight bin	Weight range	Assigned dose (BID)	Capsule strength (as assigned)	Dose reduction possibility (BID)	Reduced capsule strength
1	13.5 to < 23.0 kg	50 mg	25 mg (2x)	25 mg	25 mg (1x)
2	23.0 to < 33.5 kg	75 mg	25 mg (3x)	50 mg	25 mg (2x)
3	33.5 to < 57.5 kg	100 mg	100 mg (1x) or 25 mg (4x)	75 mg	25 mg (3x)
4	≥57.5 kg	150 mg	150 mg (1x) or 25 mg (6x)	100 mg	100 mg (1x) or 25 mg (4x)

The dose was assigned based on the patient's weight at baseline. At subsequent visits, the dose was to be adjusted for any changes of the patient's weight resulting in a change of body weight bin. Dose reductions (according to Table 14) as well as dose interruptions were allowed to manage adverse events.

PK was similar between 6 to < 12-year-old children and 12 to < 18-year-old adolescents following the proposed weight-based dosing regimen. The applied weight-based dosing scheme for nintedanib led to similar exposure in paediatric patients as in adult patients treated with a flat dose of 150 mg nintedanib BID (Table 14). The pre-defined weight-bin based paediatric dosing regimens are therefore considered by the applicant to be adequate to achieve nintedanib exposures in children and adolescents similar to those previously shown to be efficacious in the adult patient population.

3.3.2 Discussion on clinical pharmacology

Study 1199-0463: Relative bioavailability

The study design and methods used for the relative bioavailability study (1199-0463) were acceptable. The results demonstrated similar relative bioavailability of the two capsule strengths (100 mg and 25 mg) since the gMean ratios of AUC and Cmax were clearly contained within the bioequivalence limits of 80% to 125%. As such, similar nintedanib exposure would be achieved after administration of the same dose using either 25 mg or 100 mg strength capsules. The SmPC section 5.2 was updated to reflect updated data.

Population PK and PK/PD Analyses

The population PK and PK/PD models are based on paediatric data from studies InPedILD and InPedILD-ON up to 31 May 2023, including 42 and 48 paediatric patients for PK and PD, respectively. For these analyses, models from previous analyses based on data from adult patients with IPF, SSc-ILD and PF-ILD other than IPF, were used as priors.

Population PK analysis

The methods used for model development and evaluation are acceptable. Data exclusions were detailed and acceptable. The use of the adult PK model as a prior is considered acceptable given the limited data available in paediatric patients and since no major differences in PK between children aged 6 years and over and adults are expected provided body weight is appropriately accounted for in the model.

The final popPK model for nintedanib was a one-compartment model with a lag-time followed by first-order absorption and a first-order elimination from the central compartment. Body weight was included as a covariate on apparent clearance and apparent volume of distribution. This supports the use of weight-adjusted dosing of nintedanib in paediatric patients. In addition, covariate effects of Korean and other ethnicities, SSc-ILD and LDH at baseline on relative bioavailability (Frel) were included in the final model. However, the impact of these covariates on nintedanib exposure are not considered of great enough magnitude to warrant dose adjustment. An additional covariate of paediatric age on IOV Frel was identified: IOV Frel was higher in young paediatric patients than in adolescent patients close to 18 years of age, and adult patients. However, this covariate was only included to describe the available paediatric data and has no physiological impact.

The majority of PK parameters (fixed and random effects) in the final model were estimated with satisfactory precision (all RSE<42%). The IIV terms were associated with reasonable shrinkage values (all <31%). The GOF plots showed that the model described the data adequately. The VPCs indicated that the model captured the global trend of the concentration vs time data reasonably well. Overall, the final model is deemed adequate for deriving individual PK parameters (EBEs) and PK exposure metrics to be used in the subsequent paediatric PK/PD modelling analyses.

Proposed paediatric dosing regimens

The therapeutic window for nintedanib in paediatric patients has not been defined. Therefore, paediatric dosing regimens were selected to match the exposures observed in adult patients considered to be efficacious (following administration of nintedanib 150 mg BID). It is noted that, in some cases, paediatric exposures do not fully match observed adult exposures.

In paediatric patients without liver impairment, popPK-based exposure comparisons showed that, on average, paediatric patients are predicted to have higher and lower C_{max} and C_{trough} at steady state, respectively, than adult patients but similar AUC, at the proposed paediatric dose regimens. Whilst the MAH argues that no correlation between higher $C_{max,ss}$ exposure and an increase in adverse events has been established, it cannot be ruled out, since the available paediatric data are too limited. In addition, further refinement of paediatric dosing regimens is not possible because the smallest unit dose of nintedanib is 25 mg, which is administered twice daily. Therefore, it is agreed that the proposed paediatric dosing regimens provide the best match to target exposures in adult patients.

In paediatric patients with mild liver impairment (Child-Pugh class A), the use of an adjusted weight-based dosing regimen is agreed since it results in similar variability in paediatric patients as compared to adults. However, model predictions suggest that some paediatric patients, particularly those of low to intermediate weight, will have higher Cmax than the highest Cmax in adults. The MAH contends that whilst some paediatric patients with mild liver impairment will have higher C_{max} values than seen in

adult patients even after the recommended dose reduction, no safety issue would be anticipated, as no safety concerns in relation to treatment of nintedanib was identified in the paediatric patient population in trials 1199-0337 and –0378, despite some patients having observed $C_{max,ss}$ values higher than adult patients. However, only 42 paediatric patients in total were included in those trials. It is agreed that a lower starting dose for children with mild liver impairment is not possible because the smallest unit dose of nintedanib is 25 mg, which is administered twice daily, and the proposed dose reduction by one step provides the best match to target exposures in adult patients with mild liver impairment.

PK/PD analyses

The PKPD models were based on paediatric data from studies InPedILD (1199-0337) and InPedILD-ON (1199-0378). Paediatric model development used adult PKPD models as priors.

The final paediatric PKPD models for %predicted FVC and FVC Z-score were characterised by linear models describing the response on placebo (annual rate of decline) and Emax models describing a disease-modifying effect of nintedanib Ctrough,ss on the annual rate of decline in the lung function parameters. Model diagnostics for the final paediatric population PKPD models indicated a satisfactory predictive performance in general.

Emax and EC50 values were estimated with acceptable precision in the %predicted FVC model (RSE 12% and 28%, respectively). The observed geometric mean $AUC_{\tau,ss}$ (geometric coefficient of variation) exposures were 175 ng/mL·hr (85.1%) and 167 ng/mL·hr (83.6 %) in 10 patients aged 6 to 11 years old and 23 patients aged 12 to 17 years old, respectively.

Exposure-response analyses of the data of study InPedILD indicated an Emax-like relationship between exposure and FVC % predicted as well FVC Z-score, supported by adult data. For FVC % predicted, the EC50 was 4.4 ng/mL (relative standard error: 28.6%), while for FVC Z-score, the EC50 was 5.0 ng/mL (relative standard error: 75.3%).

Children (6 to less than 12 years old) showed a slower rate of decline for %predicted FVC, with a placebo slope close to zero (-0.781 %/year), compared with adolescent and adult patients, where there was a clear decline in %predicted FVC, with placebo slopes of -4.74 %/year and -4.78 %/year, respectively. For FVC Z-score, the statistically significant difference in annual rate of decline between paediatric and adult patients was found to be in the range of the inter-subject variability (increasing with decreasing paediatric age). This suggests that young paediatric patients with growing lungs behave differently from adults (and adolescents) on %predicted FVC, in terms of the annual decline on placebo. However, the limited paediatric data on placebo is not sufficient to establish with certainty how this difference is best described. For both PD endpoints, the paediatric data did not formally disagree ($p>0.05$) with the starting assumption that certain nintedanib Ctrough,ss exposure leads to the same improvement over placebo in adults and children. but the studies were not powered for efficacy. Therefore, the lack of statistical evidence for a difference in efficacy (difference from placebo in annual rate of decline) between paediatric and adult patients cannot be seen as robust evidence for similar efficacy between paediatric and adult patients.

The use of prior information from adults for establishing the PKPD relationship in paediatric patients is questioned because of the apparent differences between paediatric and adult patients, most notably in the disease progression. Moreover, the VPCs of the presented model suggest that the disease progression is not well captured in the placebo arm and that the model is overestimating the variability. To better understand the influence of the adult priors in the model and to unequivocally establish the ER in paediatric patients, the MAH presented the results of a paediatric only (minimal) PKPD/ER model. However, this model was unstable with poor parameter estimates due to insufficient paediatric data. The paediatric model results showed that the adult prior considerably influences the

PKPD/ER model. Therefore, based on the PKPD model, a conclusion of similarity in the ER relationship of nintedanib between children and adults cannot be made.

In conclusion, the pre-defined weight-bin based paediatric dosing regimens are considered adequate to achieve nintedanib exposures in children and adolescents similar to those previously shown to be efficacious in the adult patient population.

Exposure-safety correlation for selected safety markers

The relationship between exposure and liver enzyme (ALT and AST) elevations as well as the occurrence of diarrhoea was assessed descriptively using pooled data from 1199-0337 and 1199-0378 up 31-May-2023.

Whilst there was no apparent difference in nintedanib exposures (Ctrough,ss and Cmax,ss) between paediatric patients with and without diarrhoea events or liver enzyme elevations, there were too few data in paediatric patients to allow any conclusions to be drawn.

2.6.3. Conclusions on clinical pharmacology

In conclusion, the systemic exposures of nintedanib in paediatric patients 6 to 17 years old with ILDs following the proposed dosing regimens for the paediatric patients were, in general, shown to be comparable to adult patients with ILDs following the approved 150 mg BID dosing regimen.

2.6.4. Clinical efficacy

2.6.4.1. Introduction

The present submission applies to the use of nintedanib (Ofev) as treatment in paediatric patients with fibrosing interstitial lung diseases.

This submission contains data from an application originally submitted in September 2022 subsequently withdrawn in February 2023, at D120 milestone of the procedure and also additional safety and efficacy data of the ongoing open-label trial 1199-0378 (DLP 31 May 2023), presented as pooled analyses with the 1199-0337 data in addition to all data from trial 1199-0337 alone. Evidence for efficacy is derived from the placebo-controlled period of trial 1199 0337. The pooled descriptive, uncontrolled efficacy data from trials 1199-0337 and 1199-0378 are included for additional information. A data lock point was performed on 31 May 2023 and where available, selected exploratory efficacy data from trial 1199-0378 was pooled with data from trial 1199-0337 for a combined analysis presented in this application.

This exploratory efficacy data in paediatric patients was supported by an extrapolation analysis using an estimated treatment effect on FVC % predicted over 24 weeks in adults with IPF, other PF-ILDs, and SSc-ILD to infer efficacy in paediatric patients with fibrosing ILDs. Please also see pharmacology section.

2.6.4.2. Dose-response studies

No dose response studies were performed.

2.6.4.3. Main study(ies)

Study #1 identifier 1199-0337

Title: InPedILD: A double blind, randomised, placebo-controlled trial to evaluate the dose-exposure and safety of nintedanib per os 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

Methods

This was a multicentre, multinational, prospective clinical trial including a 6-month (24 weeks) randomised, placebo-controlled, double-blind period (Part A) to evaluate the dose-exposure and safety of nintedanib on top of standard of care in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD followed by an open-label period (Part B) with active treatment.

The trial consisted of 2 parts. In Part A, patients were to receive either nintedanib or placebo as randomised treatment for 24 weeks. After completion of Part A, patients were to switch to open-label nintedanib (Part B) and to remain on treatment until the end of the trial or until premature treatment discontinuation. The duration of treatment in Part B was variable from patient to patient, depending on the timepoint when the patient had entered the trial.

The end of Part B marked the end-of-treatment (EoT). For patients receiving trial medication until the end of the trial, participation in the separate open-label extension trial 1199-0378 was to be offered. Trial 1199-0337 had been ongoing at the time of finalising the main analysis CTR (Version 1); the last patient had completed the trial at the time of the CTR revision (Version 2).

Study Participants

At least 30 male and female children and adolescents (6 to 17 years old, including at least 20 adolescents aged 12 to 17 years) with documented clinically significant fibrosing ILD were planned to be randomised in approximately 24 countries. About 70 trial sites were expected to enrol 1 to 2 patients. However, it was expected that some of the trial sites might not be able to randomise any patients.

Patients under the age of 6 years were excluded from the current trial. This was based on the potential higher risk of nintedanib administration, limited evidence to support the scientific rationale of potential benefit of nintedanib, and challenges in evaluating potential clinical benefit as established in adults in children younger than 6 years.

Main inclusion criteria

Patients had to meet the following criteria:

- Children and adolescents aged 6 to 17 years at (Study) Visit 2
- Patients with evidence of fibrosing ILD on HRCT within 12 months of (Study) Visit 1 as assessed by the investigator and confirmed by central review
- Patients with FVC % predicted ≥25% at (Study) Visit 2
- Patients with clinically significant disease at (Study) Visit 2, as assessed by the investigator based on any of the following criteria:
    - Fan score ≥3 , or

- Documented evidence of clinical progression over time based on either
  - a 5-10% relative decline in FVC % predicted accompanied by worsening symptoms, or
  - a ≥10% relative decline in FVC % predicted, or
  - increased fibrosis on HRCT, or
  - other measures of clinical worsening attributed to progressive lung disease (e.g. increased oxygen requirement, decreased diffusion capacity).

Evidence of fibrosing ILD

Determination of fibrosing ILD on HRCT by the investigator was based on clinical evaluation. However, given the lack of published guidelines regarding imaging criteria for the diagnosis of fibrosing lung disease in children, central review confirmation to determine eligibility were based on pre-defined imaging criteria to ensure consistency. The imaging criteria had been determined by expert consensus and were included in the imaging manual provided to trial sites.

For patients with previous pathological findings of fibrosis on lung biopsy, fibrosis on HRCT was confirmed if at least 1 of the following imaging criteria had been met within 12 months of the screening visit (Visit 1) based on central review:

- Reticular abnormality,
- Traction bronchiectasis,
- Architectural distortion, or
- Honeycombing.

Cystic abnormalities or ground glass opacity as co-existing features were acceptable. Coexisting multifocal non-fibrotic, non-dependent consolidations (such as organising pneumonia, infection) were not allowed.

In this context, any of the following biopsy findings or diagnoses were accepted as documentation of fibrosis as confirmed by central review:

- Nonspecific interstitial pneumonia (NSIP), fibrosing,
- Usual interstitial pneumonia (UIP),
- Evidence of interstitial fibrosis on a significant component of the lung biopsy (significance assessed by the central reviewer),
- Evidence of lobular remodelling on a significant component of the lung biopsy (significance assessed by the central reviewer),
- Honeycomb lung.

For patients without any documented lung biopsy or whose biopsy results did not meet the biopsy criteria for fibrosis listed above, at least 2 of the following imaging findings were required on at least 2 HRCT scans (with the most recent one being within 12 months of Visit 1):

- Reticular abnormality,
- Traction bronchiectasis,
- Architectural distortion with/without ground glass opacification,

- Honeycombing,
- Cystic abnormality.

Main exclusion criteria

Patients were not allowed to participate in this trial if they met any of the following criteria:

- AST and/or ALT >1.5x upper limit of normal (ULN) at Visit 1
- Bilirubin >1.5x ULN at Visit 1
- Creatinine clearance <30 mL/min calculated by Schwartz formula at Visit 1.
- Patients with underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment) at Visit 1
- Previous treatment with nintedanib
- Other investigational therapy received within 1 month or 5 half-lives (whichever was shorter but ≥1 week) prior to Visit 2
- Significant pulmonary arterial hypertension (PAH) defined by any of the following:
    - Previous clinical or echocardiographic evidence of significant right heart failure
    - History of right heart catheterisation showing a cardiac index ≤2 L/min/m²
    - PAH requiring parenteral therapy with epoprostenol/treprostinil
- Other clinically significant pulmonary abnormalities, based on the opinion of the investigator
- Any of the following cardiovascular diseases:
    - Severe hypertension, uncontrolled under treatment, within 6 months of Visit 1.
    - Uncontrolled hypertension was defined as following:
        - In children 6 to ≤12 years old: ≥95th percentile + 12 mm Hg or ≥140/90 mm Hg (whichever was lower; systolic or diastolic blood pressure equal to or greater than the calculated target value)
        - In adolescents 13 to 17 years old: systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg
    - Myocardial infarction within 6 months of Visit 1
    - Unstable cardiac angina within 6 months of Visit 1
- Any of the following bleeding risks:
    - Known genetic predisposition to bleeding
    - Patients who required Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)
    - High dose antiplatelet therapy (Note: Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device [e.g. enoxaparin 4000 I.U. subcutaneous per day], as well as prophylactic use of antiplatelet therapy [e.g. acetylsalicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy] were not prohibited.)
- History of haemorrhagic central nervous system (CNS) event within 12 months of Visit 1

- Any of the following within 3 months of Visit 1:
    - Haemoptysis or haematuria
    - Active gastrointestinal (GI) bleeding or GI ulcers
    - iii.Major injury or surgery (investigator's judgment)
- Any of the following coagulation parameters at Visit 1:
    - International normalised ratio (INR) >2
    - Prolongation of prothrombin time (PTT) >1.5x ULN
    - iii.Prolongation of activated partial thromboplastin time (aPTT) >1.5x ULN
- History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1
- Known hypersensitivity to the trial medication or its components (i.e. soya lecithin)
- Patients with documented allergy to peanut or soya
- Life expectancy for any concomitant disease other than ILD <2.5 years (investigator's assessment)
- Female patients being pregnant, nursing, or planning to become pregnant while in the trial
- Patients with any diagnosed growth disorder such as growth hormone deficiency or any genetic disorder that is associated with short stature (e.g. Turner Syndrome, Noonan Syndrome, Russell-Silver Syndrome) and/or treatment with growth hormone therapy within 6 months before Visit 2. Patients with short stature which was considered to be due to glucocorticoid therapy by the investigator could be included.
- Patients <13.5 kg of weight at Visit 1 (same threshold to be used for male and female patients)

Treatments

The investigational medicinal products were nintedanib soft capsules (150 mg, 100 mg, and 25 mg) as well as matching placebo capsules.

The sizes of the commercially available 100 mg and 150 mg capsules were considered suitable for the targeted age-range. However, for patients who were unable to swallow the commercially available form, a multiple of the 25 mg capsule was proposed as an alternative administration strategy for the 100 mg or 150 mg doses.

Selection of doses in the trial

Table 15: Dose assignment and dose reduction possibilities based on body weight bins according to ICH E11

Body weight bin	Weight range	Assigned dose (bid)	Capsule strengths (as assigned)	Dose reduction possibility (bid)	Reduced capsule strengths
1	13.5[1] to <23.0 kg	50 mg	25 mg (2x)	25 mg	25 mg (1x)
2	23.0 to <33.5 kg	75 mg	25 mg (3x)	50 mg	25 mg (2x)
3	33.5 to <57.5 kg	100 mg	100 mg (1x) or 25 mg (4x)	75 mg	25 mg (3x)
4	≥57.5 kg	150 mg	150 mg (1x) or 25 mg (6x)	100 mg	100 mg (1x) or 25 mg (4x)

1 Patients with a weight <13.5 kg were excluded from the trial.

Treatment was to be interrupted in case a patient experienced a weight decrease to <13.5 kg. Treatment could be resumed when the patient's weight reached again the threshold of 13.5 kg.

In case of pathological findings identified on follow-up bone imaging or stunted growth identified on follow-up dental imaging, treatment was to be interrupted, the patient case presented to the Study Monitoring Committee (SMC) by the sponsor, and recommendations for next steps obtained. Treatment could be resumed upon recommendation of the Study Monitoring Committee.

If a patient experienced a drug-related AE, the dose could be reduced to the next lower dose and the dose could be re-started after recovery.

Dose could be reduced without prior interruption, i.e. immediately by stepping down from one dose to the next dose. 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.

Concomitant therapy

Therapeutic anticoagulation or high-dose antiplatelet therapy

Patients receiving full-dose therapeutic anticoagulation or high-dose antiplatelet therapy (such as acetylsalicylic acid >325 mg/day, or clopidogrel >75 mg/day, or equivalent doses of other antiplatelet therapy) were not eligible for participation in the trial.

Use of P-gp and CYP3A4 inducers and inhibitors

Co-administration with oral doses of a potent P-gp and CYP3A4 inducers (such as rifampicin, carbamazepine, phenytoin, and St. John's wort) may decrease exposure to nintedanib and was to be avoided.

Nintedanib is a substrate of P-gp and, to a minor extent, of CYP3A4. Co-administration with oral doses of a potent P-gp and CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cyclosporine) may increase exposure to nintedanib. In such cases, patients were to be monitored closely.

Objective

The main objectives of this trial were the evaluations of dose-exposure and safety of nintedanib in children and adolescents with fibrosing ILD.

Outcomes/endpoints

The primary objectives were assessments of

- PK based on $AUC_{T,ss}$ (with samples taken at Weeks 2 and 26) and
- Safety based on the number of patients with treatment-emergent AEs at Week 24.

No primary or key secondary efficacy endpoints were defined in trial 1199-0337. The following secondary and further efficacy endpoints were assessed.

Secondary efficacy endpoints

- Change from baseline in FVC % predicted at Weeks 24 and 52
- Absolute change from baseline in Paediatric Quality of Life QuestionnaireTM (PedsQLTM) at Weeks 24 and 52
- Change from baseline in oxygen saturation (SpO2) on room air at rest at Weeks 24 and 52
- Change from baseline in 6MWT at Weeks 24 and 52
- Patient acceptability based on the size of capsules at Week 24
- Patient acceptability based on the number of capsules at Week 24
- Time to first respiratory-related hospitalisation over the whole trial
- Time to first acute ILD exacerbation or death over the whole trial
- Time to death over the whole trial

Further efficacy endpoints

- N (%) of patients with increase/decrease from baseline in FVC % predicted (5-10%, >10%) at Weeks 24 and 52
- N (%) of patients with ≥4.4 point increase from baseline in PedsQLTM at Weeks 24 and 52
- N (%) of patients with >4% increase from baseline in oxygen saturation (SpO2) on room air at Weeks 24 and 52
- Change from baseline in SpO2 on room air with exertion at Weeks 24 and 52
- Absolute change from baseline in log-transformed CA-125 at Weeks 24 and 52
- Length of hospitalisation at Weeks 24 and 52
- Number of missed school days due to the disease under study at Week 24
- Absolute change from baseline in FVC z-score at Weeks 24 and 52

Due to the differing length of the observation period for individual patients, data for Weeks 24 and 52 were not available for all patients.

As trial 1199-0337 was not powered for efficacy, the exploratory efficacy data in paediatric patients from this trial was supported by extrapolation analysis methods that leverage the data collected in adult patients with fibrosing ILDs, including Bayesian analysis methods with informative priors.

Sample size

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.

For the primary evaluation of PK, including the assessment on whether nintedanib exposure at steady-state ($AUC_{T,ss}$) in paediatric patients is comparable with adult exposure, the clearance parameter had to be estimated with adequate precision. Assuming a coefficient of variation (CV) of 70.8% (based on the gCV of the apparent clearance at steady-state [CL/Fss] after extravascular administration observed in the PK meta-analysis), at least 20 actively treated patients with available PK measurements per age group (6 to <12 years; 12 to <18 years) would be needed so that the 95% CIs of nintedanib CL/Fss and therefore also of $AUC_{T,ss}$ would lie within 60% and 140% of the gMean estimate with at least 80% probability.

Based on the inclusion criteria of this trial and the preliminary feasibility assessment, it was anticipated that the trial would only be powered for the evaluation of PK in patients ≥12 years of age. PK parameters in children <12 years were collected and analysed but were expected to be limited due to small number of patients falling in that age range.

To further optimise PK assessments from the trial population, on-treatment PK sampling was planned in the patients assigned to placebo in Part A after switching to active treatment in Part B (i.e. at Week 26). Consequently, at least 30 randomised paediatric patients had the possibility of contributing to the PK assessment at the time of primary analysis, thereby increasing the sample size for the PK analysis.

Randomisation and blinding (masking)

After the assessment of all inclusion and exclusion criteria, eligible patients were to be randomised at Visit 2 (i.e. at the beginning of Part A) via interactive randomisation technology IRT. Randomisation was stratified by age group.

Within each stratum (6-<12 years; 12-<18 years), patients were randomised to double-blind treatment (nintedanib or placebo) in a 2:1 ratio. A validated randomisation software was used to generate the randomisation.

After completion of 24 weeks of blinded treatment, each patient was assigned via IRT to open-label treatment with nintedanib starting at Visit 6 (i.e. at the beginning of Part B), until end-of-treatment (EoT) or premature treatment discontinuation.

Part A of this trial was double-blinded. At DBL1, the trial was unblinded by the MAH for the main analysis of benefit-risk assessment of nintedanib in paediatric patients with clinically significant fibrosing ILD. Before unblinding at DBL1, the Coordinating Investigator delegated the principal investigator role to another investigator until the clinical staff is unblinded at DBL2. After unblinding at DBL1, the Coordinating Investigator reviewed and approved the main analysis CTR. Other investigators or site personnel as well as patients continue to remain blinded until the end of the trial and until final database lock (DBL2).

Earlier access to the randomised treatment assignments was provided to support the following processes during the trial. In order to enable early analysis of PK, selected non-trial personnel from the sponsor involved in the PK analyses were unblinded. The planned preliminary analyses were to be conducted by an independent Clinical Pharmacokineticist (iCPK) on a continuous basis and focused purely on PK. The process for unblinding as well as the trial team functions to be unblinded had been defined in the preliminary logistics and access plan. Furthermore, a dedicated database snapshot (no partial DBL) was to be generated after LPLV for the primary PK endpoint prior to DBL1 to allow for development and refinement of exposure-response models ('Fasttrack' PK/pharmacodynamic (PD)

analysis) referring to FVC % predicted and FVC Z-scores. Only personnel involved in the exposure-response analyses were to be granted access to the unblinded data before DBL1, whereas the trial team and all other functions not involved in the exposureresponse analyses were to remain blinded. The analysis plan for the exposure-response analysis as well as the trial statistical analysis plan (TSAP) were finalised and signed prior to the database snapshot for 'fast-track PK/PD analyses'. No formal interim report was generated.

Statistical methods

The main trial objectives were assessed by calculating descriptive statistics for the safety endpoints and by exploratory PK analyses. The PK, safety and efficacy endpoints as well as other assessments were compared between the treatment groups using descriptive statistics. No confirmatory testing was performed and hence no null and alternative hypotheses were defined. Any confidence intervals (CIs) computed were to be interpreted in the perspective of the exploratory character of the trial, i.e. CIs were considered as interval estimates for effects.

Statistical Analysis Plan

The Statistical Analysis Plan (version 1) is dated 09 Mar 2022. Changes in the planned analyses of the study from the clinical trial protocol were described in section 4 of the SAP. In addition, the following evaluations were added:

- A supporting efficacy analysis of the change from baseline in FVC % predicted at Week 24 by use of a Bayesian approach with a prior derived from adults was added.
- As the sitting height was measured incorrectly (i.e. total distance between the floor to the top of patient's head with the patient in a sitting position) at some trial sites, the main analysis of the respective safety endpoint included only correctly measured data (i.e. total distance between the sitting surface to the top of patient's head with the patient in a sitting position). A descriptive sensitivity analysis was to be performed on the patients with incorrectly measured sitting height.
- Additionally, a sensitivity analysis for the change in height will be conducted excluding patients with closed epiphyses at baseline.
- With respect to the change from baseline in height, a sensitivity analysis was conducted excluding patient with closed epiphyses ate baseline.
- An exploratory analysis of the change from baseline in log CA-125 at Week 24 by use of a Bayesian approach with a prior derived from adults was to be conducted.
- FVC z-score was to be analysed descriptively at Weeks 24 and 52.

Furthermore, the following changes to the analyses were introduced in the SAP:

- Dental imaging was not assessed at Weeks 12 and 36 and was therefore not be analysed at these endpoints.
- The change in calculated Fan severity score from baseline was not analysed as there was no validated algorithm for its derivation based assessments from the 6MWT.

Analysis Populations

For this trial, the following analysis sets were defined:

- The Screened set (SCS) included all patients who had signed informed consent.
- The Randomised set (RS) included all randomised patients whether treated or not.
- The Treated Set (TS) included all patients who were randomised to a treatment group and received at least 1 dose of trial medication.
- The Pharmacokinetic Parameter Analysis Set (PKS) included all patients in the TS who provided at least 1 PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of

PK or due to PK non-evaluability. Thus, a patient was included in the PKS, even if this patient contributed only 1 PK parameter value for 1 period to the statistical assessment.

Non-compartmental analyses of PK parameters were based on the PKS. All other analyses (including demographics) were based on the TS. Only disposition data was shown for the SCS.

Table 16: Patient sets analysed

	Patient set		
Class of endpoint	SCS	TS	PKS
Primary endpoint PK			X
Primary endpoint Safety		X	
Secondary endpoints		X	
Further endpoints Efficacy		X	
Further endpoints PK			X
Safety endpoints		X	
Demographic/baseline characteristics		X	
Disposition	X		

Analysis of primary PK endpoint

For the primary PK analysis, the area under the plasma concentration-time curve at steady state ($AUC_{\tau,ss}$) was calculated by non-compartmental as well as compartmental analysis and descriptive statistics were provided.

For patients receiving nintedanib in Part A, PK profiles were to be collected at Week 2 and at Week 26 (or later, if the PK visit was postponed). $AUC_{\tau,ss}$ was to be calculated based on Week 2 data. If the Week 2 value was missing, it was to be replaced by the available $AUC_{\tau,ss}$ of Week 26. For patients receiving placebo in Part A and nintedanib in Part B, $AUC_{\tau,ss}$ based on the PK profiles at Week 26 was to be used (corresponding to Week 2 on active treatment).

To account for potential dose reductions, $AUC_{\tau,ss}$ values were to be dose-normalised for the actual dose taken by the respective patient. Dose-normalised $AUC_{\tau,ss}$ for nintedanib (AUC_{τ,ss_D}) was to be summarised descriptively. In addition, $AUC_{\tau,ss}$ was to be derived using popPK modelling (for all patients with at least 1 valid PK sample).

Analysis of primary safety endpoint

For the primary safety analysis, the N (%) of patients with treatment-emergent AEs at Week 24 (i.e. during the double-blind period of the trial) was derived. The analysis was descriptive in nature.

Analyses of the secondary efficacy and safety endpoints

Analysis of continuous endpoints was descriptive in nature using a mixed model with repeated measurements (MMRM). Time-to-event endpoints were displayed descriptively using the Kaplan-Meier method. Categorical endpoints, safety and tolerability were displayed descriptively in frequency tables.

Subgroup analyses

The subgroups listed in Table 17 were investigated, provided that the actual size of the individual subgroup expression level is >20% of the treated patients. Groups that were too small for a sensible analysis were pooled in a meaningful manner or not analysed.

Table 17: Subgroup analyses – List of subgroups

	Description of study population [1]	PK analyses [1]	Efficacy analyses [1]	Safety analyses [1]
Gender (Male / Female)	X	X	X	X
Age group[2] (6-<12 years/ >=12-<18 years)	X	X	X	X
Race[3] (White / Asian / Black or African American)	X		X	X
Weight (≥13.5 and <23; ≥23 and <33.5; ≥33.5 and <57.5; ≥57.5)		X		
Underlying ILD diagnosis in groups	X		X	X
Immunosuppressant (excl. NSAIDs) use at baseline (Yes / No)	X		X	X
Corticosteroid use at baseline (Yes / No)	X		X	X
Formulation (25mg / 100mg / 150mg)		X		

[2] Please note that in France and Russia only patients >=12 years were eligible for recruitment.
[3] Please note that only single race respondents are taken into account. "American Indian or Alaska Native" patients, or patients that classify themselves as "Native Hawaiian or other Pacific Islander", are pooled with "Asian" subjects in the subgroup evaluations, due to the very low expected number of patients in those expression levels.

Interim analyses

No interim analysis was planned prior to DBL1.

The main analysis of the trial was performed based on the data up to the DBL1 DLP and was the basis for the benefit-risk assessment.

Following DBL2, all endpoints were re-analysed

Integration of prior knowledge on the treatment effect on FVC % predicted in adults in a supporting efficacy analysis within paediatric patients by use of a Bayesian approach with a prior derived from adults

Efficacy of nintedanib on change in FVC % predicted was investigated under the Bayesian statistical paradigm with an informative prior distribution which was derived from trials in adults. As FVC % predicted accounts for differences in age and height, the MAH expected this measure to be less affected by growth and better suited for extrapolation from adult to paediatric patients than FVC values in mL.

Bayesian dynamic borrowing

A Bayesian dynamic borrowing approach, including a tipping point analysis, was applied, as proposed by Best et al. (2021). This approach uses 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 a prior derived using adult data on FVC % predicted at 24 weeks from the nintedanib development progammes in IPF, SSc-ILD and PF-ILD (see below). The weight of this component in the prior distribution reflects the degree of belief in its validity for the paediatric trial data. A tipping point analysis was carried out to identify how much prior weight needed to be placed on evidence from trials in adults to establish efficacy in the paediatric population. Different weights ranging from 0% to 100% were used. An 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 of all priors used for the tipping analysis was reported.

The tipping point analysis was illustrated for a base case scenario in which the observed point estimate in the paediatric study is consistent with the prior distribution derived from trials in adults. It was further illustrated for 6 alternative scenarios to assess the sensitivity to key parameters.

For the base case scenario, a mean observed treatment effect of $\Delta=1.65$ of nintedanib on the absolute change from baseline in FVC [% predicted] at week 24 and a standard deviation of the change in both arms of 6.51 was assumed. In the alternative scenarios, the mean observed treatment effect of nintedanib on the absolute change from baseline in FVC [% predicted] at week 24 was varied as follows: $\Delta=1.0$ (Scenario S1) $\Delta=0.5$ (Scenario S2) $\Delta=0.0$ (Scenario S3) $\Delta=-0.5$ (Scenario S4, reflecting a negative observed treatment effect). The reference standard deviation for these scenarios was assumed to be identical as in the base case scenario. To account for a potential higher variability in paediatric patients, the standard deviation was inflated by the factors 1.2 (Scenario S5) and 1.3 (Scenario S6) compared to the base case scenario.

The operating characteristics of base case and six alternative scenarios were explored in simulation analyses; results were computed based on 20,000 simulate trials for every combination of scenario and weight.

As prior information on the treatment effect is included via the robust MAP prior, the false positive rate in the Bayesian setting is large. This is expected as the paediatric trial includes only 30 patients and is therefore rather small due to feasibility of performing a trial in paediatric patients with a rare disease.

The prior belief that the treatment effect observed in the trials in adult patients can be extrapolated to paediatric patients was assumed to be high. In the base case scenario, a prior weight of 56% on the adult data leads to a probability of 80% to correctly infer efficacy using 90% evidence level. This prior and evidence level was considered the main analysis, but the descriptive statistics (including median and 2.5%, 5%, 25%, 75%, 95% and 97.5% quantiles) of the posterior distributions of all priors used for the tipping analysis were reported.

Table 18: Operating characteristics (continued)

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%
S3: No true effect	0	3	6	11	21
	10	4	8	16	31
	20	5	11	23	42
	30	7	16	31	52
	40	10	21	39	61
	50	14	28	48	69
	56	16	32	53	73
	60	18	36	57	76
	70	25	45	66	81
	80	34	57	75	87
	90	49	70	85	93
	100	76	93	98	99
S4: True effect is -0.5 percentage points (negative effect)	0	2	4	7	15
	10	3	5	12	25
	20	3	8	17	35
	30	5	11	24	45
	40	7	16	33	53
	50	9	22	41	61
	56	11	26	46	66
	60	13	29	49	69
	70	19	38	58	77
	80	28	49	68	84
	90	42	63	81	90
	100	70	90	97	99

Prior derivation

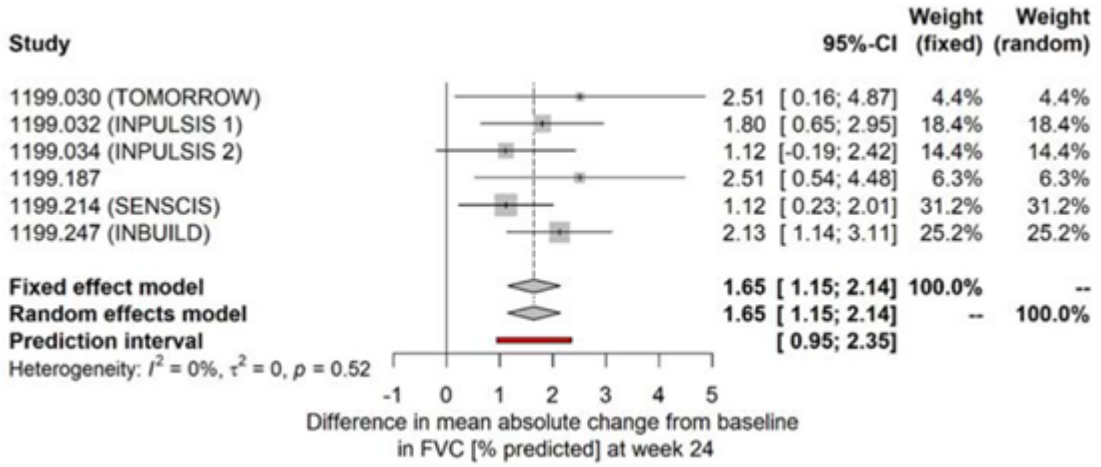
The nintedanib development program assessed changes in FVC % predicted across 6 RCTs with a duration of at least 24 weeks in adult patients with SSc-ILD, IPF and other fibrosing interstitial lung disease with progressive phenotype. The historical trial data is shown in Table 19 below.

Table 19: Historical trial data

BI study number	Study name	ClinicalTrials.gov number	N nintedanib	N placebo	N total
1199.030	TOMORROW	NCT00514683	84	84	168
1199.032	INPULSIS 1	NCT01335464	204	307	511
1199.034	INPULSIS 2	NCT01335477	217	327	544
1199.187		NCT01979952	54	54	108
1199.214	SENSCIS	NCT02597933	288	288	576
1199.247	INBUILD	NCT02999178	332	331	663

Figure 19 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 19: Historical data – meta-analysis on mean absolute change from baseline in FVC [% predicted] at week 24



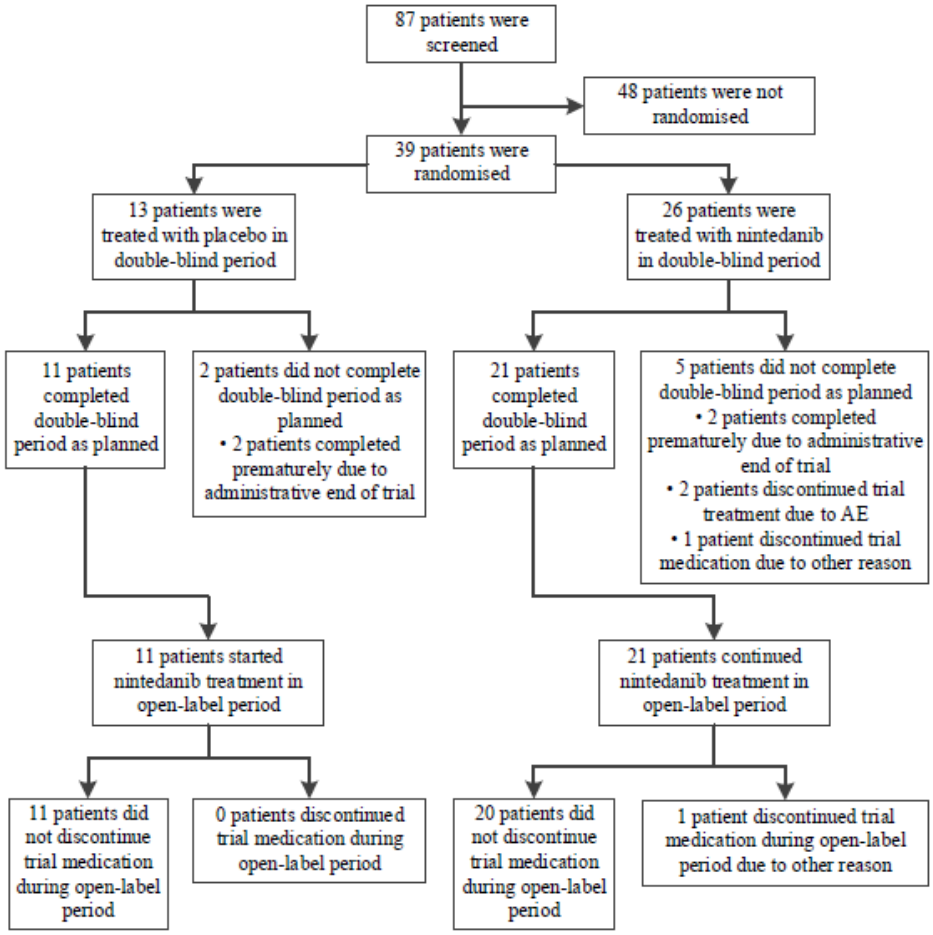
Based on these results, an informative prior was derived using the concept of MAP priors described, for example, in Neuenschwander et al. (2010) (23), Schmidli et al. (2014) (13) and Neuenschwander and Schmidli (2020). This prior was then approximated using a mixture distribution. The approximation of 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.

Results

Participant flow

Figure 20: Participant flow

Overview of disposition of patients during double-blind and open-label treatment (up to DBL2)



Recruitment

The first patient was enrolled on 27 Feb 2020; Patient recruitment stopped on 16 Feb 2022 before LPLV for the primary PK endpoint prior to DBL1 which occurred on 17 Feb 2022

A total of 87 patients were enrolled (screened) across 43 trial sites in 21 countries (Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Great Britain, Greece, Hungary, Italy, Mexico, Norway, Poland, Portugal, Russia, Spain, Ukraine, Unites States of America).

Conduct of the study

Dates of trial:

From 27 February 2020 to 24 May 2022 (last patient out)

Dates of database locks

Database lock 1: Data used for the main analysis: 11 March 2022; 36 patients were ongoing in the trial at that time

Database lock 2: 15 June 2022; all patients completed the trial

Protocol amendments

Protocol Amendment 1 (dated 19 Jun 2020)

This amendment was implemented after the first patient was enrolled into the trial. The following main changes were introduced:

• The unblinding of selected non-trial personnel from the sponsor amended following the Food and Drug Administration (FDA) recommendation to conduct an interim PK evaluation at Week 2 post-dose to ensure that the systemic exposure of nintedanib with the proposed weight-based dosing regimen in patients of 6 to 17 years of age is comparable with adults.

• information related to independence of SMC members.

• restrictions on concomitant use of potent Pgp and CYP3A4 inhibitors and inducers following an FDA recommendation.

Protocol Amendment 2 (dated 14 Jun 2021)

The following main changes were introduced by this amendment:

• information that that the first dose of the open-label trial medication of Part B (i.e. morning dose during Visit 6) was to be administered at the trial site to ensure monitoring of possible immediate adverse reactions to the patients who had received placebo during Part A

• Pathological findings identified on bone imaging and stunted growth identified on dental imaging were added to the list of AESIs to ensure expedited reporting of any cases to the pharmacovigilance group at BI and timely reporting to the SMC. Further information on treatment interruption and resumption of treatment in case of pathological findings.

• Other clarifications related to the study conduct/monitoring.

Baseline data

Demographic data

Demographic characteristics at baseline were similar in both treatment groups. Overall, there were more female (61.5%) than male (38.5%) patients. The largest proportion of patients was White (79.5%), followed by Black or African American patients (7.7%). The mean (SD) age was 12.6 (3.3) years. The majority of patients (53.8%) had a weight of ≥33.5 to <57.5 kg at baseline. The mean (SD) weight was 42.2 (17.8) kg; mean (SD) BMI-for-age z-score (BAZ) at baseline was -0.6 (1.8). Overall, none of the patients in both treatment groups were smoking. Household/second-hand smoking was reported in 10.3% of the patients (nintedanib: 3.8%, placebo: 23.1%).

Table 20: Demographic data - TS

	Placebo		Nintedanib		Total	
Number of patients (N, %)	13	100.0	26	100.0	39	100.0
Gender (N, %)						
Male	5	38.5	10	38.5	15	38.5
Female	8	61.5	16	61.5	24	61.5
Race[1] (N, %)						
White	12	92.3	19	73.1	31	79.5
Asian	0	0	2	7.7	2	5.1
Black or African American	0	0	3	11.5	3	7.7
American Indian or Alaska Native	1	7.7	1	3.8	2	5.1
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
Multiple race respondents	0	0	0	0	0	0
Ethnicity (N, %)						
Not Hispanic/Latino	8	61.5	18	69.2	26	66.7
Hispanic/Latino	5	38.5	7	26.9	12	30.8
Age [years] (mean, SD)	12.9	2.8	12.5	3.6	12.6	3.3
Age in categories [years] (N, %)						
6 to <12	4	30.8	8	30.8	12	30.8
12 to <18	9	69.2	18	69.2	27	69.2
Weight [kg] (mean, SD)	44.7	21.5	40.9	16.0	42.2	17.8
Weight in categories [kg] (N, %)						
<13.5	0	0	0	0	0	0
≥13.5 to <23.0	3	23.1	5	19.2	8	20.5
≥23.0 to <33.5	3	23.1	2	7.7	5	12.8
≥33.5 to <57.5	3	23.1	18	69.2	21	53.8
≥57.5	4	30.8	1	3.8	5	12.8
Standing height [cm] (mean, SD)	148.4	16.3	147.0	16.9	147.5	16.5
Sitting height [cm] (mean, SD)	78.5	8.3	75.4	7.3	76.3	7.5
BMI [kg/m^2] (mean, SD)	19.2	6.4	18.2	3.8	18.5	4.8
BAZ (mean, SD)	-0.7	2.4	-0.5	1.5	-0.6	1.8

BMI: body mass index; BAZ: BMI-for-age z-score
1 For each race, all respondents were counted, including those who marked additional race categories. Therefore, percentages may add up to higher than 100%.

Trial indication characteristics

Overall, the mean (SD) time since first ILD diagnosis was 5.7 (4.8) years (nintedanib: 5.0 [4.5] years, placebo: 7.1 [5.2] years). The most frequent subgroups based on the single detailed clinical ILD diagnoses (taking into account specific information reported for 'other childhood ILDs') were 'surfactant protein deficiency' (nintedanib: 26.9%, placebo: 38.5%), 'systemic sclerosis' (nintedanib: 15.4%, placebo: 23.1%), and 'toxic/radiation/drug-induced pneumonitis' (nintedanib: 11.5%, placebo 7.7%). All patients with mean time since first diagnosis of ILD in the category ≤1 year were in the nintedanib group (23.1%). All other trial indication characteristics were generally comparable across subgroups and balanced between the treatment groups.

Table 21: Trial indication characteristics - TS

	Placebo		Nintedanib		Total	
Number of patients (N, %)	13	100.0	26	100.0	39	100.0
Time since first ILD diagnosis [years] (mean, SD)	7.1	5.2	5.0	4.5	5.7	4.8
Time since first ILD diagnosis in categories [years] (N, %)						
≤1	0	0	6	23.1	6	15.4
>1 to ≤3	3	23.1	3	11.5	6	15.4
>3 to ≤5	3	23.1	6	23.1	9	23.1
>5	7	53.8	11	42.3	18	46.2
Diagnosis of ILD confirmed by surgical biopsy (N, %)						
Yes	4	30.8	9	34.6	13	33.3
No	9	69.2	16	61.5	25	64.1
Missing	0	0	1	3.8	1	2.6
Diagnosis of ILD confirmed by transbronchial biopsy (N, %)						
Yes	0	0	1	3.8	1	2.6
No	12	92.3	24	92.3	36	92.3
Missing	1	7.7	1	3.8	2	5.1
Diagnosis of ILD confirmed by HRCT[1] (N, %)						
Yes	10	76.9	22	84.6	32	82.1
No	2	15.4	4	15.4	6	15.4
Missing	1	7.7	0	0	1	2.6
Diagnosis of ILD confirmed by genetic testing (N, %)						
Yes	5	38.5	10	38.5	15	38.5
No	7	53.8	13	50.0	20	51.3
Missing	1	7.7	3	11.5	4	10.3
Underlying ILD diagnosis (N, %)						
Surfactant protein deficiency	5	38.5	7	26.9	12	30.8
cHP	0	0	2	7.7	2	5.1
Toxic/radiation/drug-induced pneumonitis	1	7.7	3	11.5	4	10.3
Post-HSCT fibrosis	0	0	1	3.8	1	2.6
Juvenile RA	0	0	1	3.8	1	2.6
Juvenile idiopathic arthritis	1	7.7	0	0	1	2.6
SSc	3	23.1	4	15.4	7	17.9
DM	0	0	1	3.8	1	2.6
Other childhood ILD[2]	3	23.1	7	26.9	10	25.6
Diagnosis confirmed by rheumatologist, in case of connective disease associated ILD (N, %)						
Yes	3	23.1	6	23.1	9	23.1
No	2	15.4	4	15.4	6	15.4
Time since confirmation by rheumatologist [years] (mean, SD)	7.7	2.70	2.8	3.10	4.5	3.71
Exposure still present, in case of exposure-related ILD[3] (N, %)						
Yes	0	0	0	0	0	0
No	0	0	5	19.2	5	12.8
Time since HSCT, in case of post-HSCT fibrosis [years] (mean, SD)	0	0	8.45	NC	8.45	NC

Table 22: Trial indication characteristics – TS- **6–<12** age group

Missing	0	0.0	0	0.0	0	0.0
Underlying ILD diagnosis (N, %)						
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	1	25.0	4	50.0	5	41.7
Chronic Hypersensitivity Pneumonitis (cHP)	0	0.0	1	12.5	1	8.3
Toxic/Radiation/Drug Induced Pneumonitis	0	0.0	1	12.5	1	8.3
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0.0	0	0.0	0	0.0
Juvenile Rheumatoid Arthritis (RA)	0	0.0	1	12.5	1	8.3
Juvenile Idiopathic Arthritis	0	0.0	0	0.0	0	0.0
Systemic Sclerosis (SSc)	2	50.0	0	0.0	2	16.7
Dermatomyositis	0	0.0	0	0.0	0	0.0
Mixed Connective Tissue Disease	0	0.0	0	0.0	0	0.0
Sarcoidosis	0	0.0	0	0.0	0	0.0
Other Childhood ILD	1	25.0	1	12.5	2	16.7
Underlying ILD diagnosis in groups (N, %)						
Surfactant Protein Deficiency	1	25.0	4	50.0	5	41.7
Chronic Hypersensitivity Pneumonitis (cHP)	0	0.0	1	12.5	1	8.3
Toxic/Radiation/Drug Induced Pneumonitis	0	0.0	1	12.5	1	8.3
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0.0	0	0.0	0	0.0
Sarcoidosis	0	0.0	0	0.0	0	0.0
Autoimmune ILDs [2] (auto)	2	50.0	1	12.5	3	25.0
Other ILDs [3] (other)	1	25.0	1	12.5	2	16.7

Table 23: Trial indication characteristics – TS- **12–<18** age group

Underlying ILD diagnosis (N, %)						
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	4	44.4	3	16.7	7	25.9
Chronic Hypersensitivity Pneumonitis (cHP)	0	0.0	1	5.6	1	3.7
Toxic/Radiation/Drug Induced Pneumonitis	1	11.1	2	11.1	3	11.1
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0.0	1	5.6	1	3.7
Juvenile Rheumatoid Arthritis (RA)	0	0.0	0	0.0	0	0.0
Juvenile Idiopathic Arthritis	1	11.1	0	0.0	1	3.7
Systemic Sclerosis (SSc)	1	11.1	4	22.2	5	18.5
Dermatomyositis	0	0.0	1	5.6	1	3.7
Mixed Connective Tissue Disease	0	0.0	0	0.0	0	0.0
Sarcoidosis	0	0.0	0	0.0	0	0.0
Other Childhood ILD	2	22.2	6	33.3	8	29.6
Underlying ILD diagnosis in groups (N, %)						
Surfactant Protein Deficiency	4	44.4	3	16.7	7	25.9
Chronic Hypersensitivity Pneumonitis (cHP)	0	0.0	1	5.6	1	3.7
Toxic/Radiation/Drug Induced Pneumonitis	1	11.1	2	11.1	3	11.1
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0.0	1	5.6	1	3.7
Sarcoidosis	0	0.0	0	0.0	0	0.0
Autoimmune ILDs [2] (auto)	2	22.2	8	44.4	10	37.0
Other ILDs [3] (other)	2	22.2	3	16.7	5	18.5

ILD included in "other ILD disease" category

Category within 'Other Childhood ILD'[1]	Randomised treatment
Desquammative Interstitial Pneumonitis	Placebo
Influenza H1N1	Placebo
Unclear (Chronic Diffuse Pulmonary Lung Disease)	Placebo
Copa Syndrome	Nintedanib
Copa Gene Mutation	Nintedanib
Undifferentiated Connective Tissue Disease	Nintedanib
Post-Infectious Bronchiolitis Obliterans	Nintedanib
Unspecified ILD	Nintedanib
Idiopathic	Nintedanib
Sting-associated Vasculopathy	Nintedanib

1 As written by the investigator on the eCRF

Table 24: Baseline characteristics – TS

	Placebo		Nintedanib		Total	
Number of patients (N, %)	13	100.0	26	100.0	39	100.0
Fan score ≥3 (N, %)						
Yes	6	46.2	17	65.4	23	59.0
No	7	53.8	9	34.6	16	41.0
Criteria for clinical progression over time (N, %)						
5-10% relative decline in FVC % predicted with worsening symptoms	3	23.1	6	23.1	9	23.1
≥10% relative decline in FVC % predicted	3	23.1	5	19.2	8	20.5
Increased fibrosis on HRCT	11	84.6	14	53.8	25	64.1
Other measures of clinical worsening	3	23.1	9	34.6	12	30.8
Has patient received or is receiving chronic treatment with glucocorticoid therapy (N? %)						
Yes	7	53.8	20	76.9	27	69.2
No	5	38.5	6	23.1	11	28.2
Missing	1	7.7	0	0	1	2.6

Source data: Table 15.1.4.1: 3 and Appendix 16.1.13.1, Table 11.4.1.3

Table 25: Fibrosis features on HRCT for all treated patients in trial 1199-0337

Underlying ILD diagnosis	Age [years]/ Gender	Day of HRCT scan	Honey combing	Reticular abnorma-lity	Traction bronchi-ectasis	Architec-tural distortion	Cystic abnorma-lity
Surfactant Protein Deficiency	6/F	-1866	-	-	-	-	X
		-1383	-	X	-	-	X
		-81	-	X	-	X	X
SSc	14/F	-567	-	X	-	-	X
		-28	-	X	-	-	X
Surfactant Protein Deficiency	7/M	-1417	-	-	-	-	X
		-1000	-	X	-	-	X
		-188	-	X	-	X	X
Surfactant Protein Deficiency	7/F	-1936	-	X	-	-	-
		-1522	-	X	-	-	X
		-216	-	X	-	-	X
SSc	15/M	-374	X	X	X	-	X
		-35	X	X	X	X	X
SSc	12/M	-179	-	X	X	X	-
		-28	-	X	X	X	-
SSc	15/F	-898	-	X	-	-	X
		-28	-	X	-	-	X
Other Childhood ILD	12/F	-716	-	X	-	-	X
		-205	-	X	-	-	X
cHP	8/M	-181	-	-	X	X	X
Surfactant Protein Deficiency	12/F	-1252	-	X	-	-	X
		-189	-	X	-	-	X
[1]/ Surfactant Protein Deficiency	12/M	-253	-	-	-	-	X
		-59	-	-	-	-	X
[2]/ Surfactant Protein Deficiency	13/F	-1113	-	-	-	-	X
		-219	-	-	-	-	X

Surfactant Protein Deficiency	17/M	-1608	-	X	-	-	X
		-964	-	X	-	-	X
		-84	-	X	-	X	X
Other Childhood ILD	13/F	-685	-	X	-	-	X
		-103	-	X	-	-	X
Toxic/Radiation/Drug Induced Pneumonitis	13/F	-192	-	X	X	-	X
		-103	-	X	X	-	X
Post HSCT Fibrosis	17/M	-83	X	-	X	X	-
		-38	X	-	X	X	-
Other Childhood ILD	13/F	-66	X	X	X	-	X
		-31	X	X	X	-	X
Surfactant Protein Deficiency	14/F	-44	-	X	-	-	X
cHP	17/F	-3676	-	X	X	X	X
		-70	-	X	-	X	X
Dermatomyositis	16/F	-959	X	X	X	-	X
		-28	X	X	X	X	X
Juvenile RA	10/F	-78	X	X	X	X	X
		-23	X	X	X	X	X

Table (con). Fibrosis features on HRCT for all treated patients in trial 1199-0337

Underlying ILD diagnosis	Age [years]/ Gender	Day of HRCT scan	Honey comb-ing	Reticular abnormal-ity	Traction bronchi-ectasis	Architec-tural distortion	Cystic abnormality
Other Childhood ILD	7/M	-1181	-	X	-	-	X
		-70	-	X	-	X	X
Toxic/Radiation/Drug Induced Pneumonitis	9/M	-722	-	X	-	-	-
		-328	-	X	-	X	-
		-7	-	X	-	X	-
[3]/ Other Childhood ILD	15/F	-332	-	-	-	-	-
		-48	-	-	-	-	-
[3]/ Surfactant Protein Deficiency	11/M	-1803	-	-	-	-	X
		-158	-	-	-	-	X
Other Childhood ILD	6/F	-360	-	X	X	X	-
		-311	-	X	-	X	-
		-87	-	X	-	X	-
SSc	16/F	-588	-	X	X	-	X
		-132	-	X	X	X	X
Surfactant Protein Deficiency	14/F	-1001	-	X	-	X	X
		-65	-	X	-	X	X
Surfactant Protein Deficiency	10/M	-569	-	X	-	X	X
		-38	-	X	-	X	X
SSc	11/F	-963	-	X	X	-	X
		-72	-	X	X	-	X
Toxic/Radiation/Drug Induced Pneumonitis	15/F	-203	-	X	-	-	-
Other Childhood ILD	15/F	-952	-	X	-	-	X
		-63	-	X	-	-	X
Surfactant Protein Deficiency	17/M	-223	-	X	-	-	X
		-42	-	X	-	-	X
Toxic/Radiation/Drug Induced Pneumonitis	13/F	-32	-	X	-	-	X
SSc	10/F	-353	-	X	-	-	X
		-11	-	X	-	-	X
Other Childhood ILD	16/M	-516	-	X	X	X	X
		-19	-	X	X	X	X
Other Childhood ILD	13/F	-532	-	X	X	-	X
		-37	-	X	X	-	X
Other Childhood ILD	17/M	-142	X	X	X	X	X
		-57	X	X	X	X	X
Juvenile Idiopathic Arthritis	15/M	-444	X	X	-	-	X
		-35	X	X	-	-	X

1 Patient [redacted] had been screened previously as Patient [redacted], with confirmed fibrosis based on HRCT showing reticular abnormality, architectural distortion, and cystic abnormality (with co-existing ground glass opacification). Due to COVID-19 hold of screening, this patient had to be re-screened, where only cystic abnormality (with co-existing ground glass opacification) was found on the same HRCT (note to file on file).
2 Patient [redacted] had been screened previously as Patient [redacted], with confirmed fibrosis based on HRCT showing reticular abnormality, architectural distortion, and cystic abnormality. Due to COVID-19 hold of screening, this patient had to be re-screened, where only cystic abnormality (with co-existing ground glass opacification) was found on the same HRCT (note to file on file).
3 Patients [redacted] and [redacted] were included in the trial based on the investigator's judgement, despite not meeting Inclusion Criterion No.4.

Baseline characteristics

In summary, the baseline characteristics were comparable between the treatment groups. Overall, the majority of patients (59.0%) had a Fan score ≥3.

The most frequent single underlying ILD diagnoses of enrolled patients were:

- 'Surfactant protein deficiency' (nintedanib: 26.9%, placebo: 38.5%),
- 'Systemic sclerosis' (nintedanib: 15.4%, placebo: 23.1%),
- 'Toxic/radiation/drug-induced pneumonitis' (nintedanib: 11.5%, placebo 7.7%).
- 'Chronic hypersensitivity pneumonitis' was reported for 2 patients (nintedanib: 7.7%).
- The remaining underlying ILD diagnoses reported for 1 patient each were:
    - Post-HSCT fibrosis,
    - Juvenile RA,
    - Juvenile idiopathic arthritis,
    - Dermatomyositis (DM),
    - Desquammative Interstitial Pneumonitis,
    - Influenza H1N1,
    - Unclear (Chronic Diffuse Pulmonary Lung Disease),
    - Copa Syndrome,
    - Copa Gene Mutation,
    - Undifferentiated Connective Tissue Disease,
    - Post-Infectious Bronchiolitis Obliterans,
    - Unspecified ILD,
    - Idiopathic
    - Sting-associated Vasculopathy.

Baseline efficacy characteristics

The mean (SD) baseline FVC was 1732.4 (937.9) mL, corresponding to 59.4 (21.9) % predicted. The mean (SD) z-score of FVC, which accounts for the differences of the lung volume due to age and gender and gives the number of standard deviations that a certain value deviates from the mean value of the reference population, was -3.5 (1.9) for the paediatric patients in this trial. The baseline efficacy variables were generally balanced across treatment groups. However, there were numerical differences between treatment groups for mean (SD) FVC (nintedanib: 1632.8 [913.5] mL, placebo: 1931.6 [991.4] mL), FVC % predicted (nintedanib: 57.7 [21.8], placebo: 62.9 [22.6]), FVC z-score (nintedanib: -3.6 [1.9], placebo: -3.2 [1.9]), and for DLCO % predicted (nintedanib: 52.9 [26.7], placebo: 63.1 [10.7]).

Table 26: Baseline efficacy data - TS

	Placebo			Nintedanib			Total		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline lung function and gas transfer									
FVC [mL]	13	1931.6	991.4	26	1632.8	913.5	39	1732.4	937.9
FVC [% predicted]	13	62.9	22.6	26	57.7	21.8	39	59.4	21.9
FVC z-score	13	-3.2	1.9	26	-3.6	1.9	39	-3.5	1.9
FEV_1/FVC	13	0.8	0.2	26	0.9	0.1	39	0.8	0.1
Oxygen saturation [%]	13	96.5	4.1	26	96.5	3.0	39	96.5	3.4
DLCO [% predicted][1]	9	63.1	10.7	18	52.9	26.7	27	56.3	22.9
Other baseline efficacy characteristics									
6MWT									
Total distance walked [m]	12	370.8	135.7	26	389.6	134.4	38	383.7	133.3
Fan severity score									
Total score	13	2.8	1.0	26	2.9	0.7	39	2.8	0.8
Missed school days since screening visit[2]									
Total number	11	2.1	6.0	23	1.1	2.3	34	1.4	3.8
Due to disease under study	11	2.1	6.0	23	0.9	2.3	34	1.3	3.8
PedsQL™ parent report									
Total score	13	64.7	20.6	25	60.4	19.1	38	61.9	19.4
PedsQL™ patient report									
Total score	12	71.6	14.4	25	66.9	14.1	37	68.4	14.2

1 Corrected for Hb; details on the calculation of DLCO % predicted are given in Section 10.3 of the CTP (Appendix 16.1.1).

2 Missed school days since screening visit correspond to the missed school days from Visit 1 to Visit 2. Home schooling related to the COVID-19 pandemic was not counted as missed school days.

Table 27: Baseline lung function and gas transfer characteristics by age group – Treated Set
Age group [years]: **6–<12**

	Placebo						Nintedanib					
	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
FVC [mL]	4	1447.3	616.7	574	1635.5	1944	8	982.8	398.6	536	879.0	1625
FVC [% predicted]	4	64.6933	17.2424	40.295	68.9920	80.494	8	56.2535	22.6322	29.360	58.9070	98.616
FEV1 / FVC	4	0.805	0.158	0.57	0.875	0.90	8	0.915	0.082	0.78	0.945	1.00
FVC z-score	4	-2.973	1.347	-4.86	-2.671	-1.69	8	-3.624	1.902	-6.00	-3.439	-0.11
Oxygen Saturation on Pulse Oximetry [%]	4	96.75	3.40	92.0	97.50	100.0	8	97.63	2.92	91.0	99.00	100.0
DLCO [% predicted] [1]	3	59.327	3.046	56.00	60.000	61.98	4	42.180	25.429	5.11	50.305	63.00

Table 28: Baseline lung function and gas transfer characteristics by age group – Treated Set
Age group [years]: **12–<18**

	Placebo						Nintedanib					
	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
FVC [mL]	9	2146.9	1078.1	548	2415.0	3478	18	1921.7	935.1	736	2034.0	4222
FVC [% predicted]	9	62.1157	25.5733	25.295	57.5920	102.770	18	58.2954	22.0941	22.225	61.8915	92.377
FEV1 / FVC	9	0.794	0.181	0.42	0.860	1.00	18	0.825	0.136	0.46	0.830	1.00
FVC z-score	9	-3.266	2.182	-6.32	-3.699	0.23	18	-3.598	1.973	-7.12	-3.200	-0.64
Oxygen Saturation on Pulse Oximetry [%]	9	96.44	4.59	85.0	98.00	100.0	18	96.06	3.00	89.0	96.50	100.0
DLCO [% predicted] [1]	6	65.020	12.878	51.00	63.110	83.90	14	55.911	27.142	15.00	50.590	120.95

Baseline pathological findings/AEs on bone imaging and dental imaging/examination

At baseline, MRIs or x-rays of growth plates as well as dental examination and x-ray for dental imaging were each conducted in 38 of the 39 treated patients. Baseline measurements of the 1 remaining patient for bone imaging (MRI) and of the 1 remaining patient for dental imaging/examination were done outside of the allowed time window up to Day 15 (i.e. at Day 16 and Day 21, respectively). Therefore, these assessments were used as baseline comparisons by the central reader/dentist but were not considered as baseline measurements for statistical analysis of pathological findings.

Bone imaging at baseline was done by MRIs for 24 patients and by x-rays for 14 patients. (see below)

Table 29: Frequency of patients with pathological findings of the epiphyseal growth plate on imaging at baseline – TS

	Placebo		Nintedanib		Total	
	N	%	N	%	N	%
Number of patients	13	100.0	26	100.0	39	100.0
Number of patients with epiphyseal growth plate imaging at baseline	12	92.3	26	100.0	38	97.4
Number of patients with at least 1 pathological finding at baseline	2	15.4	1	3.8	3	7.7
Pathological findings at the distal femur	2	15.4	0	0	2	5.1
Thickening of the epiphyses	0	0	0	0	0	0
Swelling of articular cartilage	0	0	0	0	0	0
Metaphyseal lines, if judged pathological	2	15.4	0	0	2	5.1
Other findings, if judged pathological	0	0	0	0	0	0
Pathological findings at the proximal tibia	2	15.4	1	3.8	3	7.7
Thickening of the epiphyses	0	0	0	0	0	0
Swelling of articular cartilage	0	0	0	0	0	0
Metaphyseal lines, if judged pathological	2	15.4	1	3.8	3	7.7
Other findings, if judged pathological	0	0	0	0	0	0

Pathological findings of the epiphyseal growth plate were based on central review and not on investigator decision. A patient may be counted in more than 1 category.

Table 30: Frequency of patients with pathological findings on dental examination or imaging at baseline – TS

	Placebo		Nintedanib		Total	
	N	%	N	%	N	%
Number of patients	13	100.0	26	100.0	39	100.0
Number of patients with dental examination at baseline	12	92.3	26	100.0	38	97.4
Number of patients with dental imaging at baseline	12	92.3	26	100.0	38	97.4
Dental examination						
Patients with pathological finding at baseline	7	53.8	12	46.2	19	48.7
Dental imaging						
Patients with impacted permanent teeth	5	38.5	13	50.0	18	46.2
Patients with extra/supernumerary teeth	2	15.4	1	3.8	3	7.7
Patients with additional findings[1]	1	7.7	5	19.2	6	15.4
Other findings	5	38.5	7	26.9	12	30.8

Pathological findings on the dental examination were based on dentist assessment; pathological findings on dental imaging were based on central review. A patient may be counted in more than 1 category.

1 Additional findings comprised cyst present, abscess present, solid lesion present, bone abnormality present.

Table 31: Frequency of patients with AEs connected to the epiphyseal growth plate on imaging at baseline – TS

Safety topic/	Placebo		Nintedanib		Total	
Preferred term	N	%	N	%	N	%
Number of patients	13	100.0	26	100.0	39	100.0
Growth plate disorders	2	15.4	0	0	2	5.1
X-ray limb abnormal	2	15.4	0	0	2	5.1

Only AEs with an onset date after start of treatment up to Day 15 of the safety topics 'growth plate disorder' and 'impact on growth' are displayed in this table. Please refer to Section 12.1.2.7.4 for information on all treatment-emergent AEs in those safety topics. A patient may be counted in more than 1 category.

Table 32: Frequency of patients with AEs connected to dental imaging/examination at baseline – TS

Safety topic/	Placebo		Nintedanib		Total	
Preferred term	N	%	N	%	N	%
Number of patients	13	100.0	26	100.0	39	100.0
Dental disorders	6	46.2	9	34.6	15	38.5
Dental caries	3	23.1	7	26.9	10	25.6
Tooth impacted[1]	2	15.4	2	7.7	4	10.3
Malpositioned teeth	1	7.7	1	3.8	2	5.1
Tooth development disorder[1]	1	7.7	1	3.8	2	5.1
Dental plaque	0	0	1	3.8	1	2.6
Malocclusion	0	0	1	3.8	1	2.6
Supernumerary teeth	1	7.7	0	0	1	2.6
Tooth abscess	0	0	1	3.8	1	2.6
Tooth fracture	0	0	1	3.8	1	2.6
Tooth development disorders	4	30.8	3	11.5	7	17.9
Tooth impacted[1]	2	15.4	2	7.7	4	10.3
Tooth development disorder[1]	1	7.7	1	3.8	2	5.1
Supernumerary teeth	1	7.7	0	0	1	2.6

Concomitant therapies

Baseline therapies were any therapies with a start date before the first trial drug intake and taken at least until the day of the first trial drug intake. On-treatment concomitant therapies were those which started between first and last trial drug intake (included), while any therapies with a start date after the last trial drug intake and before trial completion were defined as post-study.

The use of concomitant therapies at baseline was balanced across the treatment groups. The most commonly used therapies at baseline were ‘drugs interacting with CYP3A’ with 89.7% of overall patients (nintedanib: 84.6%, placebo: 100%;). Overall, immunosuppressant drugs were used by 82.1% of patients (nintedanib: 80.8%, placebo: 84.6%), whereas monoclonal antibodies (7.7% versus 23.1%) and non-biologic DMARDs (50.0% versus 69.2%) were used by a higher percentage of patients in the placebo than in the nintedanib group. In addition, 33.3% of patients (nintedanib: 34.6%, placebo: 30.8%) used corticosteroids.

Table 33: Baseline therapies with an incidence of at least 10% in preferred name in the total group, by CDG and preferred name – TS

CDG	Placebo		Nintedanib		Total	
Preferred name	N	%	N	%	N	%
Number of patients	13	100.0	26	100.0	39	100.0
Anti-infectives	7	53.8	9	34.6	16	41.0
Hydroxychloroquine	6	46.2	6	23.1	12	30.8
Azithromycin	4	30.8	7	26.9	11	28.2
Antihypertensives	3	23.1	4	15.4	7	17.9
Amlodipine	1	7.7	3	11.5	4	10.3
Biologic DMARDs	3	23.1	2	7.7	5	12.8
Tocilizumab	2	15.4	2	7.7	4	10.3
Corticosteroids	4	30.8	9	34.6	13	33.3
Prednisone	2	15.4	5	19.2	7	17.9
Drugs for gastric acid related disorders	3	23.1	9	34.6	12	30.8
Omeprazole	2	15.4	4	15.4	6	15.4
Drugs for obstructive airway disease	8	61.5	17	65.4	25	64.1
Prednisone	2	15.4	5	19.2	7	17.9
Salbutamol	5	38.5	1	3.8	6	15.4
Drugs interacting with CYP3A	13	100.0	22	84.6	35	89.7
Azithromycin	4	30.8	7	26.9	11	28.2
Prednisone	2	15.4	5	19.2	7	17.9
Omeprazole	2	15.4	4	15.4	6	15.4
Amlodipine	1	7.7	3	11.5	4	10.3
Drugs interacting with P-gp	10	76.9	18	69.2	28	71.8
Azithromycin	4	30.8	7	26.9	11	28.2
Prednisone	2	15.4	5	19.2	7	17.9
Omeprazole	2	15.4	4	15.4	6	15.4
Immunomodulatory medication for ILD	4	30.8	6	23.1	10	25.6
Mycophenolate Mofetil	3	23.1	5	19.2	8	20.5
Immunostimulant drugs	6	46.2	13	50.0	19	48.7
Colecalciferol	3	23.1	6	23.1	9	23.1
Vitamin D NOS	2	15.4	4	15.4	6	15.4
Immunosuppressant drugs	11	84.6	21	80.8	32	82.1
Hydroxychloroquine	6	46.2	6	23.1	12	30.8
Mycophenolate Mofetil	3	23.1	5	19.2	8	20.5
Prednisone	2	15.4	5	19.2	7	17.9
Tocilizumab	2	15.4	2	7.7	4	10.3
Monoclonal antibodies	3	23.1	2	7.7	5	12.8
Tocilizumab	2	15.4	2	7.7	4	10.3
Non-biologic DMARDs	9	69.2	13	50.0	22	56.4
Hydroxychloroquine	6	46.2	6	23.1	12	30.8
Mycophenolate Mofetil	3	23.1	5	19.2	8	20.5

In the analysis of all concomitant therapies (baseline, on-treatment and post-study drug discontinuation therapies) over the double-blind period up to DBL1, the most commonly used therapies were 'drugs interacting with CYP3A' with 89.7% of overall patients (nintedanib: 88.5%, placebo: 92.3%). Antidiarrheal medication was taken by 7.7% of overall patients (nintedanib: 11.5%, placebo: 0%).

Over the double-blind period up to DBL2, there were no significant differences with respect to the most commonly used therapies compared with those observed up to DBL1. 'Drugs interacting with CYP3A' were used by all patients in the placebo group, increasing its usage for all patients in total to 92.3%.

Table 34: All concomitant therapies with an incidence of at least 10% in preferred name in the total group for the double-blind period up to DBL2, by CDG and preferred name – TS

CDG	Placebo		Nintedanib		Total	
Preferred name	N	%	N	%	N	%
Number of patients	13	100.0	26	100.0	39	100.0
Anti-infectives	7	53.8	12	46.2	19	48.7
Hydroxychloroquine	6	46.2	6	23.1	12	30.8
Azithromycin	4	30.8	9	34.6	13	33.3
Antihypertensives	3	23.1	4	15.4	7	17.9
Amlodipine	1	7.7	3	11.5	4	10.3
Biologic DMARDs	3	23.1	2	7.7	5	12.8
Tocilizumab	2	15.4	2	7.7	4	10.3
Corticosteroids	4	30.8	10	38.5	14	35.9
Prednisone	2	15.4	6	23.1	8	20.5
Drugs for gastric acid related disorders	4	30.8	12	46.2	16	41.0
Omeprazole	2	15.4	4	15.4	6	15.4
Calcium Carbonate	2	15.4	2	7.7	4	10.3
Lansoprazole	0	0	4	15.4	4	10.3
Drugs for obstructive airway disease	8	61.5	18	69.2	26	66.7
Prednisone	2	15.4	6	23.1	8	20.5
Salbutamol	5	38.5	2	7.7	7	17.9
Drugs interacting with CYP3A	13	100.0	23	88.5	36	92.3
Azithromycin	4	30.8	9	34.6	13	33.3
Prednisone	2	15.4	6	23.1	8	20.5
Omeprazole	2	15.4	4	15.4	6	15.4
Paracetamol	1	7.7	4	15.4	5	12.8
Amlodipine	1	7.7	3	11.5	4	10.3
Lansoprazole	0	0	4	15.4	4	10.3
Drugs interacting with P-gp	10	76.9	20	76.9	30	76.9
Azithromycin	4	30.8	9	34.6	13	33.3
Prednisone	2	15.4	6	23.1	8	20.5
Omeprazole	2	15.4	4	15.4	6	15.4
Lansoprazole	0	0	4	15.4	4	10.3
Drugs used in pain therapies	6	46.2	10	38.5	16	41.0
Ibuprofen	1	7.7	5	19.2	6	15.4
Paracetamol	1	7.7	4	15.4	5	12.8
Immunomodulatory medication for ILD	5	38.5	6	23.1	11	28.2
Mycophenolate Mofetil	4	30.8	5	19.2	9	23.1
Immunostimulant drugs	8	61.5	16	61.5	24	61.5
Colecalciferol	3	23.1	6	23.1	9	23.1
Tozinameran	3	23.1	3	11.5	6	15.4
Vitamin D NOS	2	15.4	4	15.4	6	15.4

Table continues on next page

CDG	Placebo		Nintedanib		Total	
Preferred name	N	%	N	%	N	%
Immunosuppressant drugs	12	92.3	22	84.6	34	87.2
Hydroxychloroquine	6	46.2	6	23.1	12	30.8
Mycophenolate Mofetil	4	30.8	5	19.2	9	23.1
Prednisone	2	15.4	6	23.1	8	20.5
Ibuprofen	1	7.7	5	19.2	6	15.4
Tocilizumab	2	15.4	2	7.7	4	10.3
Monoclonal antibodies	3	23.1	3	11.5	6	15.4
Tocilizumab	2	15.4	2	7.7	4	10.3
Non-biologic DMARDs	11	84.6	13	50.0	24	61.5
Hydroxychloroquine	6	46.2	6	23.1	12	30.8
Mycophenolate Mofetil	4	30.8	5	19.2	9	23.1
NSAIDs	4	30.8	6	23.1	10	25.6
Ibuprofen	1	7.7	5	19.2	6	15.4
Vaccines	4	30.8	5	19.2	9	23.1
COVID-19 vaccines[1]	4	30.8	3	11.5	7	17.9

Additional information regarding background therapies provided with responses to the original procedure.

There are no approved treatments or treatments proven efficacious for fibrosing ILD in the paediatric patients population. However, due to the high unmet medical need and because of the potential to treat underyling systemic disease components (e.g. in autoimmune-associated ILDs), use of concomitant corticosteroids or immunosuppresants was not restricted in the trial.

There is no evidence for the efficacy of corticosteroids or immunosuppressants in the treatment of paediatric fibrosing ILD and therefore an impact of its use on the exploratory efficacy results was not expected.

The use of corticosteroids and immunosuppressants was balanced between groups. Corticosteroids were used by 34.6% of patients randomised to nintedanib and 30.8% of patients randomised to placebo at baseline and by 38.5% (nintedanib) and 30.8% (placebo) during the double blind period (including baseline, on–treatment and post–study drug discontinuation therapies)

Over the whole trial (including baseline, on–treatment and post–study drug discontinuation therapies), 46.2% of patients received corticosteroids in both treatment groups.

Immunosuppressants were used by 80.8% (nintedanib) and 84.6% (placebo) of patients at baseline and 84.6% (nintedanib) and 92.3% (placebo) during the double-blind period.

Over the whole trial, 96.2% (nintedanib/nintedanib) and 100.0% (placebo/nintedanib) of patients received immunosuppressants.

Data on the use of mycophenolate and tocilizumab in adult patients with fibrosing ILD associated with Systemic Sclerosis indicate a beneficial effect on FVC. It is unclear, whether these effects can be extrapolated to paediatric patients with fibrosing ILD given the lack of appropriately designed clinical studies.

Overall, concomitant use of mycophenolyte and tocilizumab was low and balanced across treatment groups.

At baseline, mycophenolate was used by 5 patients in the nintedanib group (19.2%) and 3 patients in the placebo group (23.1%), tocilizumab was used by 2 patients in the nintedanib group (7.7%) and 2 patients in the placebo group (15.4%).

Over the double-blind treatment period, mycophenolate was used by 5 patients in the nintedanib group (19.2%) and 4 patients in the placebo group (30.8%), tocilizumab was used by 2 patients in the nintedanib group (7.7%) and 2 patients in the placebo group (15.4%).

Over the whole trial (including baseline, on–treatment and post–study drug discontinuation therapies), mycophenolate was used by 6 patients randomised to nintedanib (23.1%) and 4 patients randomised to placebo (30.8%); tocilizumab was used by 2 patients randomised to nintedanib (7.7%) and 2 patients randomised to placebo (15.4%).

Only 2 patients newly started treatment with mycophenolate during the study. One patient started this concomitant therapy during placebo treatment (Table 35) and the other patient after discontinuation of nintedanib treatment. In addition, one patient adapted the dose of mycophenolate mofetil during nintedanib treatment). All other patients with these treatments were on stable mycophenolate and/or tocilizumab treatment throughout the study.

Table 35: Patients with concomitant Mycophenolate and/or Tocilizumab use

Underlying ILD diagnosis	Age [years]	Randomised treatment	Start of open-label nintedanib	Last trial drug intake	Concomitant medication (dose)	Start date of CM	End date of CM
Systemic Sclerosis	10	Placebo	Day 166	Day 541	Myophenolate mofetil (1250 mg QD)	Ongoing	Day 390
					Myophenolate mofetil (750 mg BID)	Day 397	Ongoing
					Tocilizumab (162 mg weekly)	Ongoing	Ongoing
					Salbutamol (90 µg/ inhalation)	Ongoing	Ongoing
Other childhood ILD (COPA gene mutation)	15	Nintedanib	Day 169	Day 353	Myophenolate mofetil (500 mg QD)	Ongoing	Ongoing
					Salbutamol (2 puffs/ inhalation)	Ongoing	Ongoing
Systemic Sclerosis	11	Placebo	Day 172	Day 309	Myophenolate mofetil (3.2 mL BID)	Ongoing	Ongoing
					Tocilizumab (240 mg every 4 weeks)	Ongoing	Ongoing
Systemic Sclerosis	16	Nintedanib	Day 171	Day 248	Myophenolate mofetil (750 mg BID)	Ongoing	Ongoing
Other childhood ILD (chronic diffuse pulmonary lung disease)	7	Placebo	n.a.	Day 67	Myophenolate mofetil (100 mg QD)	Day 15	Ongoing
Dermatomyositis	16	Nintedanib	Day 171	Day 360	Myophenolate mofetil (750 mg BID)	Ongoing	Ongoing
Chronic hypersensitivity pneumonitis	8	Nintedanib	n.a.	Day 102	Myophenolate mofetil (500 mg BID)	Day 475	Ongoing
Systemic Sclerosis	15	Placebo	Day 169	Day 184	Myophenolate mofetil (500 mg BID)	Ongoing	Ongoing
Systemic Sclerosis	14	Nintedanib	Day 169	Day 421	Myophenolate mofetil (1.5 mg QD)	Ongoing	Ongoing
Other childhood ILD (undiff. connective tissue disease)	13	Nintedanib	n.a.	Day 59	Tocilizumab (400 mg every 8 weeks)	Ongoing	Ongoing
					Tocilizumab (320 mg every 8 weeks)	Ongoing	Ongoing
Systemic Sclerosis	15	Nintedanib	Day 169	Day 184	Tocilizumab (8 mg/kg every 4 weeks)	Ongoing	Ongoing

In addition, bronchodilators (such as salbutamol) could have impacted FVC measurements. However, as in the clinical development programmes of adult patients with fibrosing ILDs, their use was restricted during visits with FVC measurements. If treated with bronchodilators, a wash-out period of 24 hours for long-acting and 8 hours for short-acting bronchodilators was to be observed before spirometry.

At baseline salbutamol was used by 5 patients in the placebo group (38.5%) and 1 patient in the nintedanib group (3.8%). Other respiratory medications frequently used for e.g. concomitant obstructive lung disease, such as formoterol, montelukast and tiotropium were used by 2 (7.7%) patients each in patients randomised to nintedanib, aminophylline was used in 1 patient (7.7%) randomised to placebo, budenoside/formoterol fumarate was used by 1 patient (3.8%) randomised to nintedanib, cromoglicate natrium and epinephrine were used by 1 patient (3.8%) each in patients randomised to nintedanib, fluticasone propionate in combination with salmeterol was used by 2 patient (7.7%) randomised to nintedanib, salmeterol was used by 1 patient (3.8%) randomised to nintedanib.

Over the whole trial, salbutamol was used by 6 patients randomised to placebo (46.2%) and 3 patients in the group randomised to nintedanib (11.5%); formoterol, ipratropium bromide, and montelukast were each used by 2 (7.7%) patients randomised to nintedanib, tiotropium bromide was used by 3 patients (11.5%) randomised to nintedanib, aminophylline was used in 1 patient (7.7%) randomised to placebo, a combination of budenoside and formoterol fumarate was used in 2 patients (7.7%) randomised to nintedanib; cromoglicate natrium and epinephrine were used by 1 patient (3.8%) each in patients randomised to nintedanib, fluticasone propionate in combination with salmeterol were used in 1 patient (7.7%) randomised to placebo and 2 patients (7.7%) randomised to nintedanib, and salmeterol was used used by 1 patient (3.8%) randomised to Nintedanib.

No important protocol deviation was noted for the washout restriction related to bronchodilators.

Numbers analysed

Table 36: Patient analysis sets at DBL1 – SCS

	Placebo[1]		Nintedanib[1]		Total	
	N	%	N	%	N	%
Screened set (SCS)					87	
Randomised set (RS)	13	100.0	26	100.0	39	100.0
Treated set (TS)	13	100.0	26	100.0	39	100.0
Pharmacokinetic set[2] (PKS) at DBL1	9	69.2	22	84.6	31	79.5
Pharmacokinetic set[2] (PKS) at DBL2	11	84.6	24	92.3	35	89.7

1 Treatment as randomised at the beginning of Part A

2 Patients in the placebo were only part of the PKS once they provided PK endpoints after their switch to open-label nintedanib treatment in Part B

Outcomes and estimation

Efficacy analyses were conducted on the TS. While the sample size was sufficient for the evaluation of the primary objectives of the trial (PK and safety), the trial was not powered for the evaluation of efficacy endpoints like FVC %- predicted. Therefore, efficacy data in this trial were considered exploratory and supportive.

Efficacy data are provided in total and per treatment. When assessing efficacy data for later time points (i.e. Weeks 26, 36, and 52 or over the whole trial), it has to be considered that patients randomised to placebo received placebo for the first 24 weeks (double-blind period), followed by nintedanib treatment for the remaining weeks (open-label period), whereas patients randomised to nintedanib received solely nintedanib throughout the whole trial (double-blind and open-label periods). For the Week 26, 36, and 52 time points and the whole trial period, the respective treatment groups are called placebo/nintedanib and nintedanib/nintedanib.

Primary endpoint

No primary efficacy endpoint was evaluated in this trial.

Secondary endpoints

Change from baseline in FVC % predicted at Weeks 24 and 52

Primary analysis

Based on data up to DBL1, the adjusted mean change from baseline to Week 24 in FVC % predicted was larger in the nintedanib group (1.25, 95% CI -1.08, 3.57) than in the placebo group (0.34, 95% CI -2.98, 3.67). The adjusted mean difference between the treatment groups was 0.90 (95% CI -3.18, 4.98), suggesting that nintedanib treatment may lead to an improvement in FVC % predicted compared with placebo.

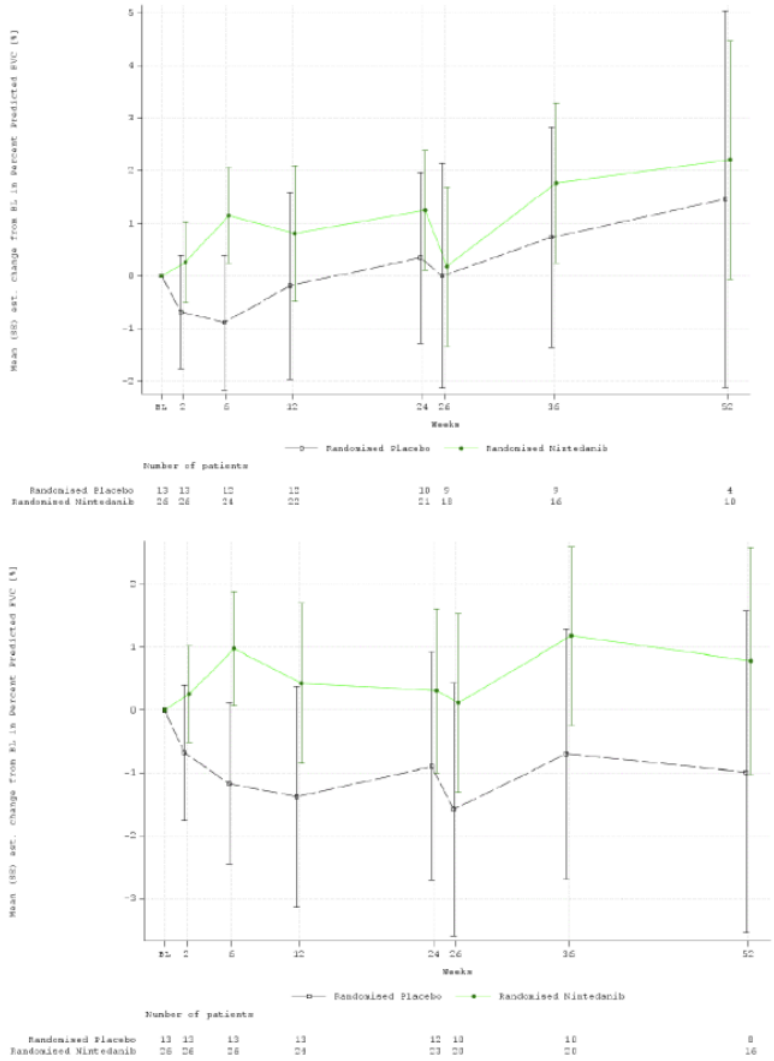
In line with the data up to DBL1, analysis of all data of the double-blind period up to DBL2 yielded an adjusted mean difference between the treatment groups (nintedanib versus placebo) of 1.21 (95% CI -3.40, 5.81) at Week 24 suggesting that nintedanib treatment may lead to an improvement in FVC % predicted compared with placebo. During the 28 weeks of nintedanib treatment in the open-label period, the change from baseline in FVC % predicted remained relatively constant, resulting in the adjusted mean difference between the treatment groups (nintedanib/nintedanib versus placebo/nintedanib) of 1.77 (95% CI -4.70, 8.25) at Week 52 being similar to the value at Week 24 (i.e. at the end of the double-blind period).

It should be noted that the patient numbers were low and the inter-patient variability of the FVC assessments was large, leading to wide 95% CIs. As a result, confidence intervals of the adjusted mean changes overlap between the 2 treatment groups for all assessed time points.

Table 37: Adjusted mean (SE) of absolute change in FVC % predicted from baseline at Weeks 2, 6, 12, 24, 26, 36, and 52 (up to DBL2) – TS

Visit/ treatment	N	Change from baseline to visit				Comparison to placebo[1]			
		Adjusted mean[2]	SE	95% CI		Adjusted mean[2]	SE	95% CI	
				Lower	Upper			Lower	Upper
Week 2									
Placebo	13	-0.68	1.08	-2.88	1.52				
Nintedanib	26	0.26	0.77	-1.30	1.82	0.94	1.33	-1.76	3.64
Week 6									
Placebo	13	-1.17	1.28	-3.78	1.44				
Nintedanib	26	0.98	0.91	-0.87	2.83	2.15	1.58	-1.07	5.36
Week 12									
Placebo	13	-1.38	1.76	-4.95	2.20				
Nintedanib	24	0.43	1.27	-2.15	3.01	1.81	2.18	-2.61	6.23
Week 24									
Placebo	12	-0.89	1.81	-4.61	2.82				
Nintedanib	23	0.31	1.31	-2.36	2.98	1.21	2.25	-3.40	5.81
Week 26									
Placebo/ nintedanib	10	-1.58	2.02	−5.72	2.56				
Nintedanib/ nintedanib	20	0.12	1.42	-2.80	3.03	1.70	2.48	-3.37	6.76
Week 36									
Placebo/ nintedanib	10	-0.70	1.99	−4.76	3.37				
Nintedanib/ nintedanib	20	1.19	1.42	−1.72	4.09	1.88	2.46	−3.13	6.90
Week 52									
Placebo/ nintedanib	8	-0.98	2.56	−6.26	4.30				
Nintedanib/ nintedanib	16	0.79	1.81	−2.95	4.53	1.77	3.14	−4.70	8.25

Figure 21: Adjusted mean (SE) of absolute change from baseline in FVC % predicted over 52 weeks (upper panel: up to DBL1; lower panel: up to DBL2) - TS



The change from baseline in FVC % predicted was investigated for the following subgroups: Age, gender, immunosuppressant use (excluding NSAIDs), corticosteroid use at baseline

Secondary endpoint -Absolute change from baseline in Paediatric Quality of Life Questionnaire

(PedsQL) at Weeks 24 and 52

Health-related quality of life was assessed using the PedsQLTM questionnaire, which was to be filled out by the patient as well as the patient's parent/legal guardian.

Parent assessment

Based on the PedsQLTM parent assessment (total score) up to DBL1, health-related quality of life improved slightly from baseline to Week 24 in both treatment groups with an adjusted mean change of 5.04 (95% CI -0.43, 10.51) in the nintedanib group and 4.30 (95% CI -3.27, 11.87) in the placebo group. The adjusted mean difference between the treatment groups was 0.74 (95% CI -8.63, 10.11).

The results for the PedsQLTM parent assessment (total score) based on data up to DBL2 showed an adjusted mean change of 5.48 (95% CI 0.38, 0.38) in the nintedanib group and 5.62 (95% CI -1.51, 12.74) in the placebo group. The adjusted mean difference between the treatment groups was -0.13 (95% CI -8.98, 8.71).

An adjusted mean change from baseline to Week 52 in the nintedanib/nintedanib group was 7.83 (95% CI 1.80, 13.86), while for patients in the placebo/nintedanib group the adjusted mean change was 4.38 (95% CI -4.40, 13.16)

Table 38: Adjusted mean (SE) of absolute change in PedsQLTM total score (parent assessment) from baseline to Week 24 and to Week 52 (up to DBL2) – TS

		Change from baseline to visit				Comparison to placebo[1]			
Visit/		Adjusted		95% CI		Adjusted		95% CI	
Treatment	N	mean[2]	SE	Lower	Upper	mean[2]	SE	Lower	Upper
Week 24									
Placebo	11	5.62	3.48	-1.51	12.74				
Nintedanib	21	5.48	2.49	0.38	10.58	-0.13	4.32	-8.98	8.71
Week 52									
Placebo/ nintedanib	7	4.38	4.29	-4.40	13.16				
Nintedanib/ nintedanib	16	7.83	2.94	1.80	13.86	3.45	5.23	-7.25	14.16

1 For Week 24, the nintedanib group was compared to the placebo group. For Week 52, the nintedanib/nintedanib group (i.e. patients receiving nintedanib throughout the trial) was compared to the placebo/nintedanib group (i.e. patients receiving placebo for 24 weeks and nintedanib thereafter).

2 The adjusted mean is 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 analysed patients in the model (not only on patients with a measurement both at baseline and at the respective visit).

Source data: Appendix 16.1.13.1, Table 12.1.1.8

Patient assessment

Based on the PedsQLTM patient assessment (total score) up to DBL1, the adjusted mean change in health-related quality of life from baseline to Week 24 was 6.76 (95% CI 2.41, 11.10) in the nintedanib group and 4.66 (95% CI -1.38, 10.70) in the placebo group.

The results for the PedsQLTM patient assessment (total score) based on data up to DBL2 showed an adjusted mean change of 6.51 (95% CI 2.53, 10.50) in the nintedanib group and 5.48 (95% CI -0.05, 11.02) in the placebo group. The adjusted mean difference between the treatment groups was 1.03 (95% CI -5.85, 7.91).

An adjusted mean change from baseline to Week 52 in the nintedanib/nintedanib group was 1.24 (95% CI -4.60, 7.08), while for patients in the placebo/nintedanib group the adjusted mean change was 0.90 (95% CI -7.62, 9.42).

Secondary endpoint- Change from baseline in oxygen saturation (SpO2) on room air at rest at Weeks 24 and 52

Oxygen saturation (SpO2) was assessed following a rest of at least 5 min on room air.

Based on data up to DBL1, oxygen saturation at rest was maintained from baseline to Week 24 under nintedanib treatment (adjusted mean change: -0.01, 95% CI -1.37, 1.35), while it slightly decreased in patients receiving placebo (adjusted mean change: -1.15, 95% CI -3.08, 0.79). The adjusted mean difference between the treatment groups of 1.14 (95% CI -1.23, 3.52) was numerically in favour of nintedanib.

Based on data up to DBL2, the adjusted mean difference between the treatment groups was also numerically in favour of nintedanib.

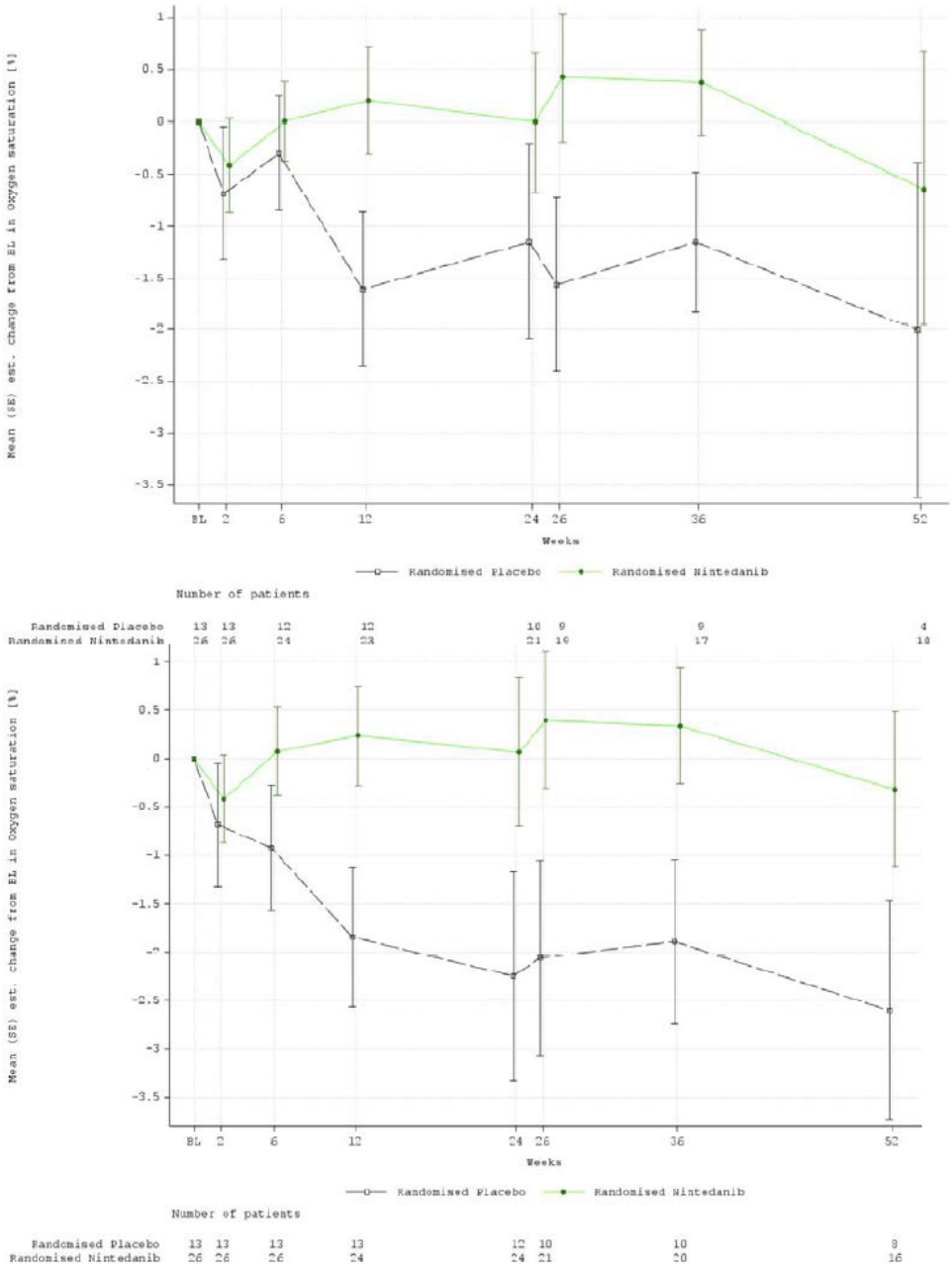
Table 39: Adjusted mean (SE) of absolute change in oxygen saturation (SpO2) on room air at rest from baseline to Week 24 and to Week 52 (up to DBL2) – TS

		Change from baseline to visit				Comparison to placebo[1]			
Visit/ treatment	N	Adjusted mean[2]	SE	95% CI Lower	95% CI Upper	Adjusted mean[2]	SE	95% CI Lower	95% CI Upper
Week 24									
Placebo	12	−2.25	1.08	−4.45	-0.04				
Nintedanib	24	0.07	0.77	−1.49	1.63	2.31	1.33	−0.39	5.02
Week 52									
Placebo/ nintedanib	8	-2.60	1.14	-5.02	-0.18				
Nintedanib/ nintedanib	16	-0.32	0.80	-2.03	1.40	2.28	1.39	-0.69	5.25

1 For Week 24, the nintedanib group was compared to the placebo group. For Week 52, the nintedanib/nintedanib group (i.e. patients receiving nintedanib throughout the trial) was compared to the placebo/nintedanib group (i.e. patients receiving placebo for 24 weeks and nintedanib thereafter).

2 The adjusted mean is 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 analysed patients in the model (not only on patients with a measurement both at baseline and at the respective visit).

Figure 22: Adjusted mean (SE) of absolute change from baseline in oxygen saturation (SpO2) on room air at rest over 52 weeks (upper panel: up to DBL1; lower panel: up to DBL2) - TS



Secondary endpoint-Change from baseline in 6-min walk distance at Weeks 24 and 52

The exercise capacity of a patient at a given time point was assessed by recording the distance covered during the 6MWT. Based on data up to DBL1, the adjusted mean difference between the treatment groups (nintedanib versus placebo) was 2.6 m (95% CI -53.1 m, 58.3 m). A similar adjusted mean difference between the treatment groups (nintedanib/nintedanib versus placebo/nintedanib) was seen at Week 52 (4.8 m; 95% CI -75.6 m, 85.2 m). Based on data up to DBL2, the adjusted mean difference between the treatment groups was 7.2 m (95% CI -50.7 m, 65.0 m) at Week 24 and -32.9 m (95% CI -103.1 m, 37.2 m) at Week 52. Given the large interpatient

variability and wide 95% CIs as well as the small number of patients in both treatment groups, the results should be interpreted with caution.

Table 40: Adjusted mean (SE) of absolute change in the 6MWT [m] from baseline to Week 24 and to Week 52 (up to DBL2) – TS

		Change from baseline to visit				Comparison to placebo[1]			
Visit/ treatment	N	Adjusted mean[2]	SE	95% CI Lower	95% CI Upper	Adjusted mean[2]	SE	95% CI Lower	95% CI Upper
Week 24									
Placebo	11	10.5	22.9	−36.4	57.3				
Nintedanib	21	17.6	16.5	−16.2	51.5	7.2	28.2	−50.7	65.0
Week 52									
Placebo/ nintedanib	7	28.1	27.6	−29.4	85.5				
Nintedanib/ nintedanib	15	-4.9	19.0	−44.5	34.7	-32.9	33.8	−103.1	37.2

1 For Week 24, the nintedanib group was compared to the placebo group. For Week 52, the nintedanib/nintedanib group (i.e. patients receiving nintedanib throughout the trial) was compared to the placebo/nintedanib group (i.e. patients receiving placebo for 24 weeks and nintedanib thereafter).

2 The adjusted mean is 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 analysed patients in the model (not only on patients with a measurement both at baseline and at the respective visit).

Secondary endpoint-Patient acceptability based on the size and number of capsules at Week 24

Secondary endpoint -Time to first respiratory-related hospitalisation over the whole trial

The overall number of events included in the analyses of respiratory-related hospitalisation over the whole trial up to DBL1 was low. Up to DBL1, 2 patients were hospitalised in the nintedanib/nintedanib group (1 patient each due to COVID-19 and due to respiratory distress/carbon dioxide increased -], while no patients in the placebo/nintedanib group were hospitalised. The first hospitalisation for both patients occurred during the double-blind treatment. In addition to the 2 patients described for DBL1, 1 patient - in the nintedanib/nintedanib group was hospitalised twice due to respiratory-related reasons during open-label treatment, comprising one stay at the hospital because of COVID-19 and another stay at the hospital because of an ILD exacerbation.

Table 41: Time to first acute ILD exacerbation or death over the whole trial Up to DBL2

	Placebo/nintedanib		Nintedanib/nintedanib	
Number of patients at risk[1] (N)	13		26	
Patients with event (N, %)	0	0	3	11.54
Patients censored[2] (N, %)	13	100.0	23	88.46

1 Number at patients at risk corresponds to the cumulative number of patients having entered the respective time interval.

2 Censoring rules can be found in Table 5.2.2.11: 1 of the TSAP (Appendix 16.1.9).

Time to death over the whole trial

Up to DBL1, no deaths occurred in this trial. Likewise, no deaths were reported up to DBL2.

Additional efficacy endpoints

N (%) of patients with increase or decrease from baseline to Week 24 and to Week 52 in FVC % predicted (5-10%, >10%)

Patients were categorised based on their absolute increase and decrease from baseline to Weeks 24 and 52 in FVC % predicted using the categories <5%, ≥5% to ≤10%, and >10%.

At the time of DBL1, FVC measurements at Week 24 were not yet available for one fifth of the patients (nintedanib: 19.2%; placebo: 23.1%). For the majority of the remaining patients in both treatment groups, FVC % predicted increased or decreased by less than 5% during the first 24 weeks of treatment (nintedanib: 57.7%; placebo: 69.2%). For 4 patients (15.4%) in the nintedanib group, FVC % predicted increased by at least 5% (and less than 10%) from baseline to Week 24; 1 nintedanib patient (3.8%) had an absolute change from baseline of more than 10%. None of the placebo patients had an increase in FVC % predicted of 5% or more in the double-blind period, further supporting a positive treatment effect of nintedanib on lung function.

When comparing Week 52 with baseline (based on data up to DBL1), there were 4 patients with an increase from baseline in FVC % predicted of ≥5% to ≤10% and the 1 patient with an increase of >10% which were all in the nintedanib/nintedanib group. It should be noted that 2 thirds of the patients (nintedanib/nintedanib: 61.5%; placebo/nintedanib: 69.2%) had not yet reached Week 52 at the time of DBL1, limiting the interpretation of the data.

At the time of DBL2, FVC measurements were available for most patients at Week 24 (missing values: 11.5% in nintedanib group and 7.7% in placebo group), while 1 third of the patients (38.5% in both treatment groups) had not reached Week 52 yet. As seen up to DBL1, FVC % predicted either increased or decreased by less than 5% during the 24 weeks of double-blind treatment in the majority of the patients (nintedanib: 61.5%; placebo: 76.9%).

No additional patients with an FVC % predicted increase of at least 5% (10%) or more than 10% at Week 24 were reported up to DBL2 compared with DBL1. Following the 28 weeks of open-label nintedanib treatment (i.e. at Week 52), an increase from baseline in FVC % predicted of ≥5% to ≤10% was reported for 3 additional patients (1 patient in the nintedanib/nintedanib group and 2 patients in the placebo/nintedanib group) between DBL1 and DBL2.

Figure 23: Butterfly plot of patients with an absolute change (increase/decrease) from baseline in FVC % predicted of <5%, 5%-10%, and >10% up to DBL1 (upper panel: Week 24; lower panel: Week 52) – TS

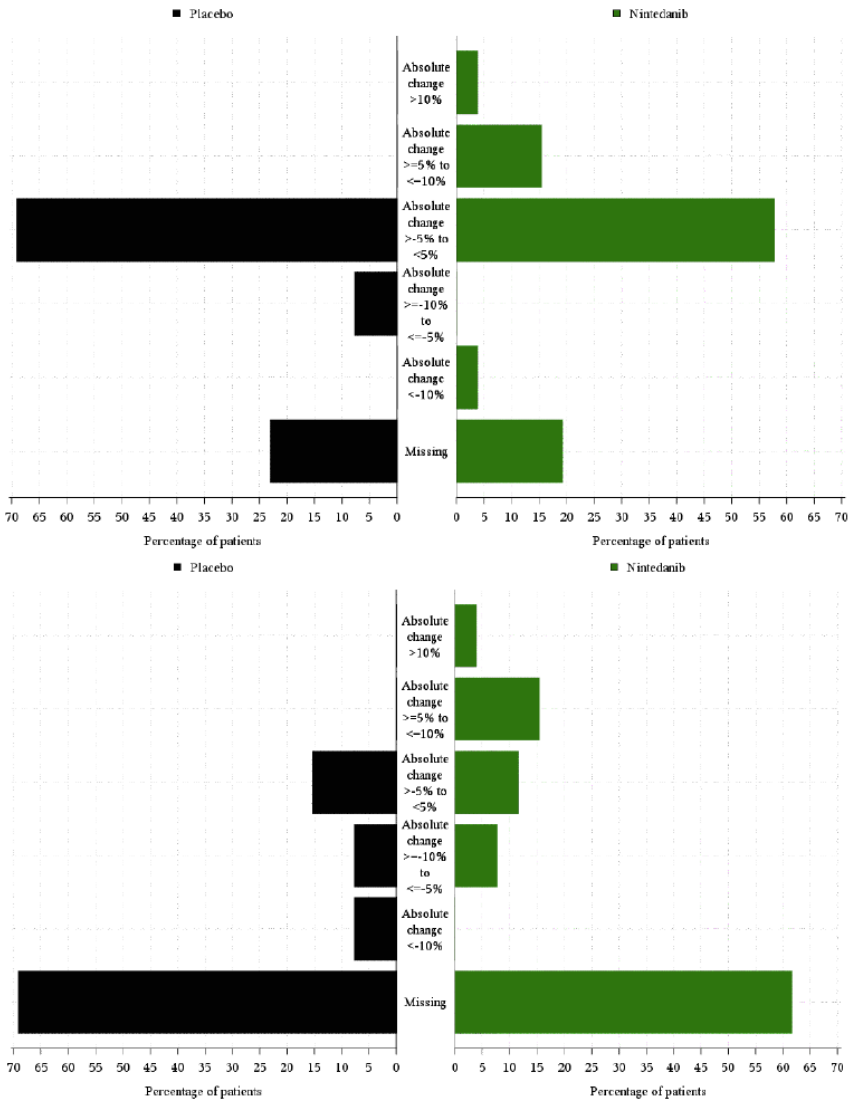
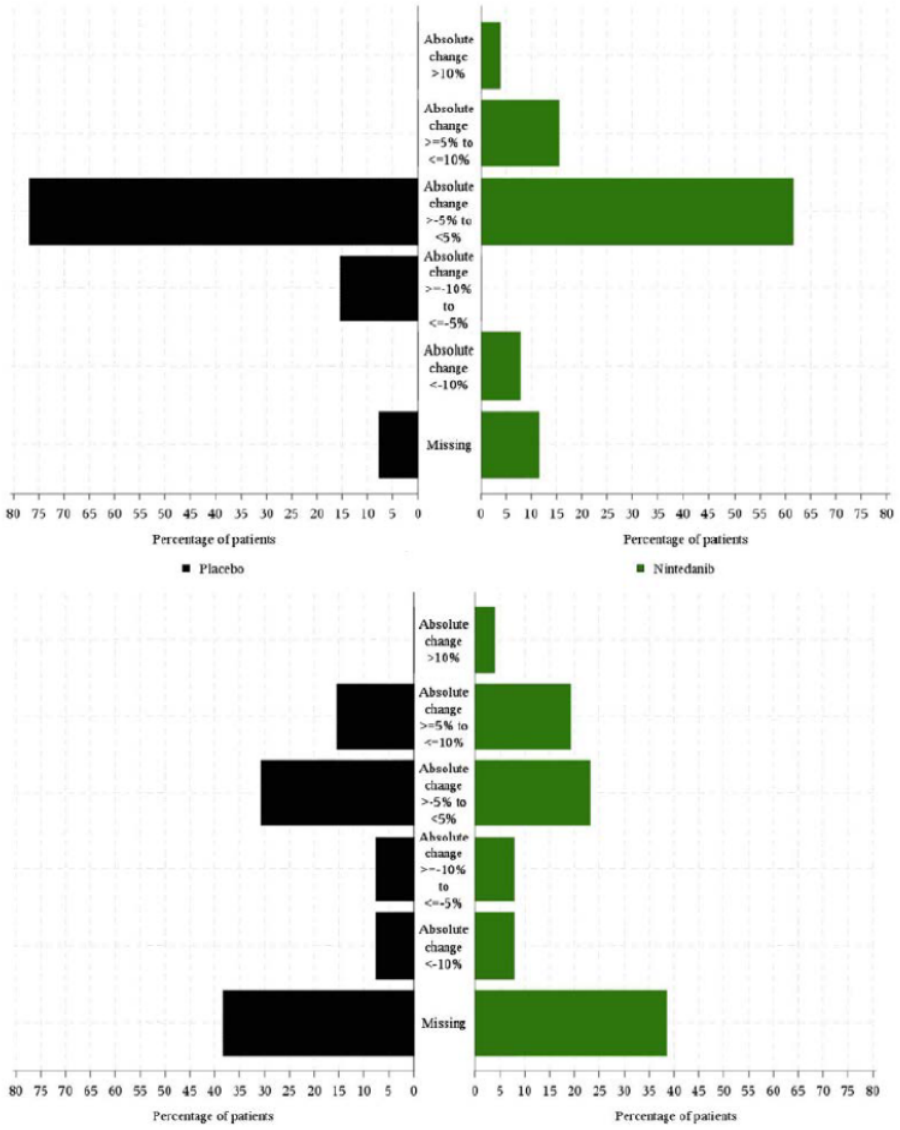


Figure 24: Butterfly plot of patients with an absolute change (increase/decrease) from baseline in FVC % predicted of <5%, 5%-10%, and >10% up to DBL2 (upper panel: Week 24; lower panel: Week 52) – TS



N (%) of patients with **≥4.4** point increase from baseline to Week 24 and to Week 52 in PedsQLTM

Patients with a ≥4.4 point increase from baseline in PedsQLTM at Week 24 were classified as Responders. Based on the parent assessment up to DBL1, 8 of 19 nintedanib patients (42.1%) and 5 of 10 placebo patients (50.0%) fulfilled this responder criterion at Week 24. As per patient assessment, 9 of 19 nintedanib patients (47.4%) and 7 of 10 placebo patients (70.0%) fulfilled this responder criterion at Week 24. Based on the very limited data available for Week 52 at DBL1, parents reported a ≥4.4 point increase from baseline in PedsQLTM for 6 of 10 nintedanib patients (60.0%) and 2 of 4 placebo patients (50.0%), while 4 of 10 nintedanib patients (40.0%) and none of the 4 placebo patients

reported such an improvement themselves . Up to DBL2, up to 3 additional patients per treatment group fulfilled the responder criterion at Week 24 and Week 52, both based on the parent and the patient assessments.

Overall, no clear benefit of nintedanib treatment on quality of life could be observed compared with placebo.

N(%) of patients with >4% increase from baseline to Week 24 and to Week 52 in oxygen saturation (SpO2) on room air at rest

Only patients with a baseline oxygen saturation of <96% and available measurements at baseline and the respective time point were included in the analysis.

Up to DBL1, 1 of 6 patients (16.7%) in the nintedanib group and none of the 2 placebo patients were classified as responder with respect to oxygen saturation at Week 24. At the time of DBL2, no additional responders had been identified. Due to the very low number of patients included in this analysis, no adjusted odds ratio could be presented. Based on the very limited data available for Week 52 at DBL1, none of the 2 patients in either treatment group had an absolute increase >4% from baseline in SpO2 on room air at rest. Likewise, no responders had been identified for Week 52 at DBL2

Change from baseline in oxygen saturation (SpO2) on room air with exertion at Weeks 24 and 52

Based on data up to DBL2, the adjusted mean SpO2 on room air with exertion increased from baseline to Week 24 by 2.69 (95% CI -0.13, 5.51) in patients receiving nintedanib treatment and by 2.66 (95% CI -1.13, 6.45) in placebo patients. The adjusted mean difference between the treatment groups was 0.03 (95% CI -4.72, 4.77). Following the open label period, the adjusted mean difference of the treatment groups (nintedanib/nintedanib versus placebo/nintedanib) at Week 52 was 2.03 (95% CI -3.81, 7.87).

Ancillary analyses

N/A

2.6.4.4. Summary of main efficacy results

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 42: Summary of efficacy for trial 1199-0337

Title: InPedILD®: A double blind, randomised, placebo-controlled trial to evaluate the dose-exposure and safety of nintedanib per os 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 identifier	1199-0337 (InPedILD®)		
Design	Phase III clinical trial in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD consisting of a randomised, placebo-controlled, double-blind treatment period, followed by an open-label active treatment period		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		24 weeks of double-blind treatment, with patients assigned to nintedanib and placebo in a 2:1 ratio Not applicable Variable treatment period beyond 24 weeks, during which all patients receive open-label nintedanib treatment until the end of the trial or until a reason for treatment withdrawal was met
Hypothesis	No confirmatory testing was performed and hence no null and alternative hypotheses were defined.		
Treatments groups	Double-blind/nintedanib		Nintedanib, 50 mg bid, 75 mg bid, 100 mg bid, 150 mg bid (by weight bin), n = 26
	Double-blind/placebo		Matching placebo, n = 13
	Open-label/randomised to nintedanib		Nintedanib, 50 mg bid, 75 mg bid, 100 mg bid, 150 mg bid (by weight bin), n = 19
	Open-label/randomised to placebo		Nintedanib, 50 mg bid, 75 mg bid, 100 mg bid, 150 mg bid (by weight bin), n = 10
Endpoints and definitions (please refer to notes on next page for further information)	Secondary endpoint	Change in FVC % predicted	Change from baseline in FVC % predicted at Week 24 and 52
	Bayesian analysis incorporating data from previous clinical trials in adult patients with fibrosing ILDs	Change in FVC % predicted	Change from baseline in FVC % predicted at Week 24
Database lock	16 Mar 2022		

Results and Analysis			
Analysis description	Main analysis		
Analysis population and time point description	All treated patients Week 24, Week 52, whole trial		
Descriptive statistics and estimate variability	Treatment group	Nintedanib	Placebo
	Number of subjects	21	10
	Change from baseline in FVC % predicted at Week 24 in paediatric patients with fibrosing ILDs Adjusted mean	1.25	0.34
	95% CI	(-1.08, 3.57)	(-2.98, 3.67)
Effect estimate per comparison	Secondary endpoint: Change from baseline in FVC % predicted at Week 24	Comparison groups	Nintedanib versus placebo
		Adjusted mean	0.90
		95% CI	(-3.18, 4.98)
	Bayesian analysis with pre-specified prior weight of 0.56: Change from baseline in FVC % predicted at Week 24	Comparison groups	Nintedanib versus placebo
		Median	1.60
		95% credibility interval	(-0.70, 3.09)
Notes	The main objectives of the trial were to evaluate dose-exposure and safety of nintedanib in paediatric patients with fibrosing ILD. No primary or key secondary efficacy endpoints were defined in trial 1199-0337. As patient numbers were low and the trial was not powered for efficacy, all efficacy analyses in this trial were considered exploratory and supportive. Results for the main secondary efficacy endpoint (change from baseline in FVC % predicted at Week 24) and the related Bayesian analysis (incorporating data from previous trials in adults with fibrosing ILDs) are included in this table.		

2.6.4.5. Analysis performed across trials (pooled analyses and meta-analysis)

Integration of prior knowledge on the treatment effect of nintedanib on FVC% predicted in adults in a supporting efficacy analysis within paediatric patients by use of a Bayesian approach with a prior derived from adults.

A Bayesian dynamic borrowing approach, including a tipping point analysis, was applied to the treatment effect of nintedanib on FVC % predicted at Week 24 using a prior derived from adults and combining it with the analysis of paediatric data, using data from trial 1199-0337 only. Descriptive statistics (including median and 2.5%, 5%, 10%, 20%, 80%, 90%, 95% and 97.5% quantiles) of the posterior distributions for selected weights used for the tipping point analysis based on data up to DBL1 are presented.

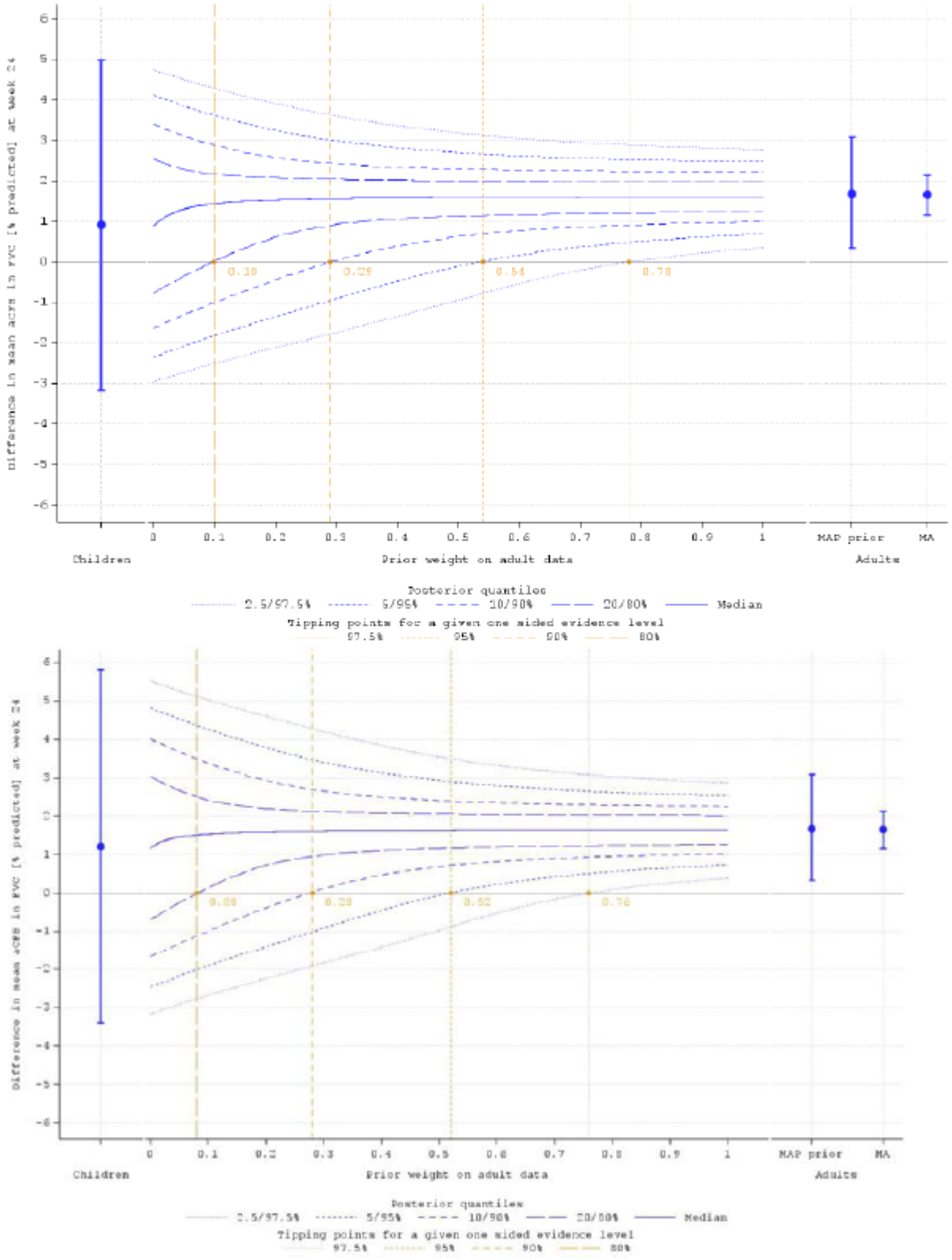
Using the pre-specified prior weight of 56% on the adult data, the Bayesian analysis of the change from baseline in FVC % predicted at Week 24 (up to DBL1) led to a median difference of 1.60 (nintedanib

compared with placebo; 95% credible interval: -0.70 to 3.09). The targeted 1-sided evidence level of 90% (i.e. the posterior probability that nintedanib is superior to placebo being at least 90%) was well achieved based on the prior weight of 56% on the adult data. Even when choosing a prior weight lower than the one pre-specified by the experts of only 10% on the adult data, a 1-sided evidence level of 80% was still achieved. This suggests that nintedanib treatment in paediatric patients with fibrosing ILD is efficacious.

Using all available data up to DBL2 and the pre-specified prior weight of 56% on adult data (see above), the Bayesian analysis yielded results comparable with the DBL1 analysis for the change from baseline in FVC % predicted at Week 24, with a median difference of 1.63 (nintedanib compared with placebo; 95% credible interval: -0.69 to 3.40). The corresponding posterior probability of nintedanib being superior to placebo was 95.5. The targeted 1-sided evidence level of 90% was achieved with a prior weight of 28% on the adult data, which is well below the pre-specified prior weight of 56%.

When choosing an even lower prior weight of only 8% on the adult data, a 1-sided evidence level of 80% was still achieved. Therefore, the data up to DBL2 is in line with the assumption based on data up to DBL1 suggesting that nintedanib treatment in paediatric patients with fibrosing ILD is efficacious.

Figure 25: Tipping point analysis for absolute change from baseline in FVC % predicted at Week 24 (upper panel: up to DBL1; lower panel: up to DBL2) – TS



Pooled analyses 2 (trials 1199-0337 and 1199-0378).

At the date of snapshot of the pooled analysis, a total of 54 patients with clinically significant fibrosing ILD had received at least one dose of nintedanib in either of the trials since the start of trial 1199-0337 27 February 2020. This consisted of 33 (61.1%) patients who had participated in both trials (30 of those patients rolled over with less than 12 weeks of transition and 3 patients with more than 12 weeks of transition), 6 (11.1%) patients who had participated only in trial 1199-0337, but not rolled-over, and 15 (27.8%) patients who had entered only into trial 1199-0378.

Overall, there were more female (59.3%) than male (40.7%) patients. The largest proportion of patients were White (77.8%), followed by Black or African American patients (9.3%). The mean (SD) age was 12.8 (3.3) years. At baseline, half of patients (50.0%) had a weight of ≥33.5 to <57.5 kg, followed by ≥57.5 kg (20.4%) and ≥13.5 to <23 kg (18.5%). The mean (SD) weight was 43.28 (18.30) kg.

Efficacy results

In this pooled analysis, exploratory efficacy was assessed based on change from baseline in FVC % predicted, absolute change from baseline in SpO2 at rest and with exertion, absolute change from baseline in Paediatric Quality of Life Questionnaire (PedsQLTM), absolute change from baseline in 6MWT and biomarker endpoint - absolute change from baseline in log-transformed CA-125. For each efficacy endpoint, only time points with available results (i.e. model converged) are listed in the in-text tables below. Only time points at which data for at least 20% of all treated patients are available are shown in the tables displayed below.

Absolute change from baseline in FVC % predicted

The adjusted mean change in FVC % predicted was -1.22 (95% CI -4.24, 1.81) from baseline to Week 52 and 0.37 (95% CI -2.35, 3.09) from baseline to Week 76. A graphical display for the adjusted mean of absolute change from baseline in FVC % predicted over time as shown below suggests that lung function is maintained up to Week 76 (the last time available) in paediatric patients with fibrosing ILD receiving weight-based dosing of nintedanib.

Table 43: Adjusted mean (SE) of absolute change from baseline in FVC % predicted over time – TS

Visit		Change from baseline to visit			
				95% CI	
	N[1]	Adjusted mean[1]	SE	Lower	Upper
Week 2	50	-0.95	1.17	-3.30	1.41
Week 6	27	-0.22	1.18	-2.66	2.22
Week 12	44	-0.48	0.92	-2.38	1.41
Week 24	31	-1.09	1.70	-4.74	2.56
Week 26	28	0.23	1.05	-1.92	2.38
Week 36	36	-0.28	1.15	-2.68	2.11
Week 52	33	-1.22	1.44	-4.24	1.81
Week 64	32	-0.85	1.53	-3.96	2.26
Week 76	27	0.37	1.31	-2.35	3.09

1 The adjusted mean is based on MMRM with fixed categorical effects 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 analysed patients in the model (not only on patients with a measurement both at baseline and at the respective visit).

Due to the design of the studies, not all time points are available for all patients.

Absolute change from baseline in oxygen saturation (SpO2) on room air at rest

Oxygen saturation (SpO2) was assessed following a rest of at least 5 min on room air. The resting oxygen saturation before first nintedanib intake was in the normal range of ⩾94% for the majority of patients. Baseline oxygen saturation ranged from 82.0% to 100.0%. The adjusted mean change of oxygen saturation at rest was 0.88 (95% CI 0.06, 1.69) from baseline to Week 52 and 0.05 (95% CI -1.07, 1.16) from baseline to Week 100.

Table 44: Adjusted mean (SE) of absolute change from baseline in oxygen saturation (SpO2) on room air at rest over time – TS

Visit		Change from baseline to visit			
				95% CI	
	N[1]	Adjusted mean[2]	SE	Lower	Upper
Week 2	52	-0.00	0.29	-0.58	0.58
Week 6	27	0.45	0.35	-0.26	1.16
Week 12	45	0.23	0.41	-0.59	1.04
Week 24	33	0.56	0.38	-0.20	1.32
Week 26	28	-0.13	0.71	-1.57	1.30
Week 36	36	0.43	0.44	-0.45	1.31
Week 52	34	0.88	0.40	0.06	1.69
Week 64	31	0.27	0.37	-0.48	1.02
Week 76	30	0.47	0.45	-0.45	1.40
Week 88	26	-0.66	0.59	-1.89	0.56
Week 100	21	0.05	0.54	-1.07	1.16

1 Based on the number of patients having available data at baseline and at the respective visit.
2 The adjusted mean is based on MMRM with fixed categorical effects 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 analysed patients in the model (not only on patients with a measurement both at baseline and at the respective visit).
Due to the design of the studies, not all time points are available for all patients.

Absolute change from baseline in oxygen saturation (SpO2) on room air with exertion

Oxygen saturation with exertion was measured during the 6MWT. As the measurement was to be done on room air, values of any patient who received supplemental oxygen and therefore did not complete the 6MWT on room air were excluded from the analysis of this endpoint. The lowest oxygen saturation measured for a given patient during the test was used for the analysis.

Overall, the oxygen saturation (SpO2) on room air with exertion was maintained over time.

The adjusted mean change of oxygen saturation with exertion was 0.99 (95% CI -1.30, 3.27) from baseline to Week 52 and 0.14 (95% CI -3.50, 3.78) from baseline to Week 100.

It should be noted that data are only available for limited number of patients (N = 16) at Week 100

Absolute change from baseline in Paediatric Quality of Life Questionnaire (PedsQLTM)

Health-related quality of life was assessed using the PedsQLTM questionnaire, which was to be filled out by the patient as well as the patient's parent/legal guardian.

Parent and patient assessment

Based on the parent and patient assessments, health-related quality of life improved slightly in the PedsQLTM total score observed. The adjusted mean change of parent assessment in PedsQLTM total score was 5.02 (95% CI 0.49, 9.55) from baseline to Week 52 and 4.46 (95% CI -1.65, 10.57) from baseline to Week 100. For patient assessment of PedsQLTM totalscore, the adjusted mean change was 1.43 (95% CI -2.47, 5.32) from baseline to Week 52 andm1.98 (95% CI -3.42, 7.38) from baseline to Week 100.

Absolute change from baseline in 6-min walk distance (6MWT)

The adjusted mean change in the 6MWT [m] was 3.0 (95% CI -26.2, 32.3) from baseline to Week 52 and 10.7 (95% CI -19.9, 41.2) from baseline to Week 100 (includingmdata from 20 patients included into the MMRM at this time point).

Table 45: Adjusted mean (SE) of absolute change from baseline in the 6MWT [m] over time - TS

Visit		Change from baseline to visit			
				95% CI	
	N[1]	Adjusted mean[2]	SE	Lower	Upper
Week 24	39	13.4	11.4	-9.6	36.4
Week 52	30	3.0	14.4	-26.2	32.3
Week 76	27	54.3	35.4	-137.3	246.0
Week 100	20	10.7	15.1	-19.9	41.2

1 Based on the number of patients having available data at baseline and at the respective visit.
2 The adjusted mean is based on MMRM with fixed categorical effects 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 analysed patients in the model (not only on patients with a measurement both at baseline and at the respective visit).
Due to the design of the studies, not all time points are available for all patients.

2.6.4.6. Supportive study(ies)

Trial 1199-0378 - long-term safety and tolerability study.

Study title: An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 2 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD-ON)

The multicentre, multinational, extension clinical trial 1199-0378 evaluates long-term safety and tolerability of nintedanib on top of standard of care in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD. In consistency with trial 1199-0337, patients below 6 years of age are not considered to be included predominantly due to safety concerns. It consists of a non-randomised, open-label nintedanib treatment period of at least 2 years.

Objective: The main objective of the trial is to assess the safety and tolerability of long-term treatment with nintedanib in pediatric patients with clinically significant fibrosing ILD.

Methods: Trial 1199-0378 is an ongoing multicentre, multinational, prospective, open-label extension trial for patients who have participated in trial 1199-0337 and did not prematurely discontinue trial medication. In addition, new patients diagnosed with clinically significant fibrosing ILD can enter trial 1199-0378 directly, when eligible. The extension trial is planned to last at least 2 years. According to the current clinical trial protocol, it will end when the last roll-over patient reaches 2 years of treatment in 1199-0378 or when alternative treatment options become or are made available outside of the clinical trial (via marketing authorization, via compassionate use, or via similar process). It is to be extended by one additional year via an upcoming clinical protocol amendment as agreed with EMA/CHMP. Final results will be submitted for assessment.

Main criteria for in- and exclusion: This trial includes patients from trial 1199-0337 who had not prematurely discontinued trial treatment (roll-over patients) and male or female children and adolescents (6 to 17 year-old) diagnosed with a clinically significant fibrosing ILD based on either

clinical markers of disease severity or evidence of clinical progression and evidence of fibrosis on high resolution computed tomography (HRCT) within 12 months prior to screening, and forced vital capacity (FVC) % predicted ≥25% at start of treatment (new patients). The exclusion criteria ensure patient safety and excludes patients with e.g. elevated liver enzymes, chronic liver disease, impaired renal function, significant pulmonary hypertension, selected cardiovascular diseases, or risk of bleeding from participating in the trial.

The first roll-over patient entered the trial on 6 Apr 2022 and the first directly enrolled patient entered the trial on 8 Apr 2022. A pooled data analysis on trials 1199-0337 and 1199-0378 was performed.

At the snapshot analysis date, the roll-over of patients from trial 1199-0337 had been completed while enrolment of new patients was still ongoing.

For the efficacy results please see the pooled analysis discussed above.

2.6.5. Discussion on clinical efficacy

This procedure consists of a line extension application for a new strength (25 mg soft capsule) and a type II variation to add a new indication for the use of nintedanib in children. This corresponds to a resubmission of the application originally submitted in 2022 but subsequently withdrawn by the MAH following receipt of Major Objections at D120 related to similarity between paediatric and adult diseases on 09 Feb 2023.

While data from the trial 1199-0337 were assessed in the previous application, this submission contains also new supplementary data i.e pooled analysis uncontrolled efficacy results from trials 1199-0337 and 1199-0378.

Data package

- Clinical trial data

This application is based on the 1199-0337 trial where only secondary or exploratory efficacy endpoints were assessed. The MAH indicated that the conduct of a confirmatory efficacy trial was deemed not feasible based on the low disease prevalence in children and therefore only a focused pharmacokinetic (PK) and safety study of nintedanib in paediatric patients in the age range of 6 to 17 years with clinically significant fibrosing ILD was performed. This is agreed by CHMP.

- Extrapolation of the data from adults

As the confirmatory efficacy trial in paediatric population was not performed the efficacy and safety is mainly claimed based on the extrapolation from adults. This approach was discussed in the PIP.

In order to extrapolate, the clinical features of fibrosing ILD between adult patients and paediatric patients should be similar.

Magnitude of benefit based on the extrapolation from adults

An adjusted mean (95% confidence interval) difference at week 24 in FVC % predicted of 1.21 (95% CI: -3.40, 5.81) in favour of nintedanib was observed in the paediatric trial -0337, however as discussed below the study was not powered to assess efficacy.

A supplementary Bayesian analysis incorporating adult data was also presented to further support demonstration of efficacy for nintedanib in the paediatric population. For the prespecified primary weight of 0.56, a median difference between nintedanib and placebo in change in FVC % predicted of 1.63 (95% credible interval: −0.69, 3.40) was observed at Week 24. The respective 90% credible interval (0.12, 2.84) and 80% credible interval (0.78, 2.37) did not include the null.

It is noted that in order for the 95% credible interval from the posterior distribution to exclude 0, a prior weight of 0.76 on the adult data is required.

Consideration of the effective sample size of robust MAP adult prior confirms the high degree of borrowing from adult data required to meet the pre-specified, as well as more stringent, decision criteria for demonstration of efficacy in the paediatric study.

A sensitivity analysis of the Bayesian extrapolation approach was provided excluding adult data of the IPF studies and excluding the patients with UIP-like fibrotic pattern in the PF-ILD study from the MAP prior. A similar degree of borrowing adult data for the original Bayesian extrapolation and the respective sensitivity analysis with regard to the effective sample size was demonstrated across a range of evidence levels. It is noted that in order for the 95% credible interval from the posterior distribution to exclude 0, a prior weight of 0.90 on the adult data is required.

Study 1199-0337

This study aimed to recruit children with clinically significant ILD with evidence of fibrosis ("fibrosing" interstitial lung diseases, which was the agreed target population in the PIP).

Evidence of fibrosis

It needs to be noted that pulmonary fibrosis is very rare in children and none of the clinical, radiological, or histological descriptions used for pulmonary fibrosis diagnosis in adult patients, especially in situations of idiopathic PF, can apply to paediatric situations. For this reason, identification of paediatric patients with "fibrosing" interstitial lung diseases is challenging. There are no widely accepted radiologic or histopathologic criteria for identification of children with lung fibrosis.

Therefore, the MAH with an external panel of experts (radiologists, clinicians and pathologists) developed criteria for the use in this study.

Evidence of fibrosing ILD in the study was determined based on pathological findings of fibrosis on lung biopsy or/and on HRCT scans results (two HRCT were required if biopsy results were not available or did not meet the biopsy criteria for fibrosis, which was the case for 10 children).

As the majority of patients in trial 1199-0337 were enrolled based on HRCT results only, the HRCT criteria used to identify patients with fibrosis was discussed extensively during the procedure. Although, the CT criteria were developed by panel of experts, they were not externally validated. In addition, literature on sensitivity and specificity of HRCT to identify lung fibrosis in children is not available. In response to this concern, the MAH using their own data (for 8 patients), determined the sensitivity as 75%. However, specificity could not be evaluated as the biopsies for patients without a confirmation of fibrosis were considered not reliable (too old).

This uncertainty is further increased by the results of a recent study indicating a low concordance between biopsy-and CT-diagnosed fibrosis in children (Birce Sunman and Nural Kiper, 2024). The uncertainty regarding the diagnosis of children with progressive fibrosing ILD is highlighted in section 4.2 together with the requirements for involvement of a multidisciplinary team in diagnosis and treatment.

Evidence of progressive disease

Clinically significant disease was defined using Fan severity score ≥3 or documented evidence of clinical progression over time (based on either a 5-10% relative decline in FVC % predicted accompanied by worsening symptoms, or a ≥10% relative decline in FVC % predicted, or increased fibrosis on HRCT, or other measures of clinical worsening attributed to progressive lung disease).

Importantly, a progressive phenotype or failure of previous treatment was not an absolute requirement for enrolment into this study, i.e. patients with clinically significant disease as defined by Fan severity score ≥3 without documented evidence of clinical progression over time could be enrolled.

Study treatment

In the trial the dose was adjusted depending on the body weight. Children with body weight 13.5 - 22.9 kg received 50 mg of nintedanib twice daily, with body weight 23.0 - 33.4 kg received 75 mg of nintedanib twice daily, with body weight 33.5 - 57.4 kg received 100 mg twice daily and children with body weight 57.5 kg and above received adult dose (i.e. 150 mg twice daily).

Study endpoints

In the 1199-0337 trial there were no primary efficacy objectives/endpoints. The applicant indicated that the conduct of a confirmatory efficacy trial was deemed not feasible based on the low disease prevalence in children. Therefore, efficacy in children is claimed based on the extrapolation of results from adult patients.The secondary efficacy endpoints investigated in the 1199-0337 study were similar to those investigated in adult studies and included an assessment of lung function (i.e. change from baseline in FVC % predicted and change from baseline in oxygen saturation (SpO2) both assessed at Weeks 24 and 52),functional capacity (i.e. 6MWT) and other clinical outcomes (i.e. time to death, time to first acute ILD exacerbation or death or time to first respiratory-related hospitalisation over the whole trial).

Study results

39 patients were randomised to double-blind treatment (nintedanib or placebo) in a 2:1 ratio. Randomisation was stratified by age group (6-11 years; 12-17 years).26 patients (6-11 years: 8 patients; 12-17 years:18) were randomised to nintedanib and 13 patients (6-11 years:4 patients; 12-17 years:9 patients) to placebo.

After completion of trial 1199-0337, patients were able to enrol into the open-label extension trial 1199-0378, which also included new patients.

Study population

Trial 1199-0337 enrolled patients with a broad spectrum of diseases. The most frequent single underlying ILD diagnoses were ‘surfactant protein deficiency’ (nintedanib: 26.9%, placebo: 38.5%), ‘systemic sclerosis’ (nintedanib: 15.4%, placebo: 23.1%), and ‘toxic/radiation/drug-induced pneumonitis’ (nintedanib: 11.5%, placebo 7.7%). Chronic hypersensitivity pneumonitis was reported for 2 patients (nintedanib: 7.7%). The remaining underlying ILD diagnoses reported for 1 patient each were post-HSCT fibrosis, juvenile RA, juvenile idiopathic arthritis, Dermatomyositis (DM), Desquammative Interstitial Pneumonitis, Influenza H1N1, Unclear (Chronic Diffuse Pulmonary Lung Disease), Copa Syndrome, Copa Gene Mutation, Undifferentiated Connective Tissue Disease, Post-Infectious Bronchiolitis Obliterans, Unspecified ILD, Idiopathic and Sting-associated Vasculopathy.

Of note, while sarcoidosis is one of the most frequent conditions associated with child ILD, no paediatric patients with sarcoidosis were enrolled in study 1199-0337.

As indicated during the AHEG meeting, some diseases investigated do not fall under the definition of ILDs (i.e. Post-Infectious Bronchiolitis Obliterans). See section 2.6.5 under additional experts’ consultation.

Concomitant therapies

There are no approved treatments or treatments proven efficacious for fibrosing ILD in the paediatric population. However, due to the high unmet medical need and because of the potential to treat underyling systemic disease components (e.g. in autoimmune-associated ILDs), use of concomitant corticosteroids or immunosuppressants was not restricted in the trial.

Therefore, many patients were taking other medications used for the treatment of ILD during the double-blind period, including corticosteroids, mycophenolate mofetil and tocilizumab.

Although the use of other therapies was balanced between the groups, their effect on the treatment outcomes is difficult to determine taking into consideration the number of additional therapies given and the small number of children per group and by ILD subtype, therefore uncertainty remains but is considered acceptable.

Efficacy results

There was no primary efficacy endpoint in this study. Only secondary efficacy exploratory endpoints were evaluated, as presented below.

Change from baseline in FVC % predicted at Weeks 24 and 52

Comparative data is available for 24 weeks. At week 24 the difference between the treatment groups was small and 95% confidence intervals included the null value, i.e. for DBL2 the adjusted mean difference between the treatment groups (nintedanib versus placebo) was 1.21 (95% CI -3.40, 5.81).

Further, inter-patient variability of the FVC assessments was large and there was variability in responses in subgroups and at different timepoints.

Change from baseline in oxygen saturation (SpO2) on room air at rest at Weeks 24 and 52.

The mean oxygen saturation of enrolled patients was 96.5% at baseline with lower value reported 85.0%. At week 24 it seems that patients on nintedanib maintained their oxygen saturation at rest whereas in patients on placebo there was some deterioration (adjusted mean of absolute change in oxygen saturation for nintedanib was 0.07 and for placebo was -2.25 at DBL2). Patients with a >4% increase from baseline in SpO2 on room air at rest at Week 24 were classified as responders. No responders had been identified for Week 52 at DBL2.

In the study, oxygen saturation was not only examined at rest but also under exertion. For this endpoint, i.e. the adjusted mean SpO2 under exertion baseline to Week 24, there was no difference between groups.

The exercise capacity of patients was assessed through the use of change from baseline in 6-min walk distance at Weeks 24 and 52 endpoints. Based on data up to DBL2, the adjusted mean difference between the treatment groups was 7.2 m (95% CI -50.7 m, 65.0 m) at Week 24 and -(minus)32.9 m (95% CI -103.1 m, 37.2 m) at Week 52. During the original procedure the MAH was requested to comment on the negative effect of nintedanib on exercise capacity seen at week 52. In the responses provided the MAH confirmed pronounced decreases from baseline to Week 52 in the distance walked were observed in individual patients. For 11 patients decrease from baseline of at least 25 m (corresponding to the minimally clinically important distance in adults) was reported.

The health-related quality of life was assessed through the use of PedsQL questionnaire (patient and parent total score) and the results do not indicate that there was a clear benefit of nintedanib treatment on quality of life compared with placebo.

Time-to-event analyses were performed in the study such as time to first respiratory-related hospitalisation over the whole trial, time to first acute ILD exacerbation or death over the whole trial

and time to death over the whole trial. The overall number of events reported in the study was low. There were no deaths over the whole study period in any treatment group.

Pooled analysis uncontrolled efficacy results from trials 1199-0337 and 1199-0378.

Pooled efficacy analyses of the combined nintedanib exposure period of trials 1199-0337 and 1199-0378 were also provided in this procedure. In this pooled analysis median exposure to nintedanib in trials 1199-0337 and 1199-0378 combined (up to 25 Aug 2023) was 78.1 weeks, corresponding to nearly twice the median exposure of trial 1199-0337 alone. The adjusted mean change in FVC % predicted was -1.22 (95% CI -4.24, 1.81) from baseline to Week 52 and 0.37 (95% CI -2.35, 3.09) from baseline to Week 76. The adjusted mean change of oxygen saturation at rest was 0.88 (95% CI 0.06, 1.69) from baseline to Week 52 and 0.05 (95% CI -1.07, 1.16) from baseline to Week 100.

In general, it is difficult to interpret changes in lung function parameters recorded in the extension study without a control group and due to the large variability.

Additional experts' consultation

The CHMP decided to convene an Ad-Hoc Expert Group (AHEG) meeting to consult experts on the following questions. The full minutes of the AHEG are provided below.

Question 1:

The Experts are invited to discuss whether the broad spectrum of fibrosing childhood interstitial lung diseases exhibit sufficient pathophysiologic similarities in fibrotic remodelling to each other to justify use of basketing approach, i.e. grouping of children and adolescents with different underlying fibrosing childhood interstitial lung diseases in a single study.

Summary: The experts acknowledged that Childhood ILD represents a group of very heterogenous diseases due to the various underlying aetiologies evolving nevertheless, towards a common fibrotic picture if fibrosis develops.

The experts agreed that it is acceptable to group children and adolescents of the age 6 to 17 with different underlying fibrosing childhood interstitial lung diseases in a single study. This was based on the common pathways of fibrosis. Accordingly, the use of a basketing approach was considered acceptable by the experts, considering also the rarity of the different childhood ILD entities.

The importance of clear criteria for fibrosis diagnosis was emphasized by the experts. All experts highlighted the importance to have a multidisciplinary team consisting of clinicians, radiologists and pathologists to make the diagnosis of lung fibrosis and its progression in children.

The diagnosis of progressive lung fibrosis follows a two-step approach. The first step is to ascertain the diagnosis of lung fibrosis, and the second step to define whether the lung fibrosis is progressive. The progression of fibrosis may depend on the underlying aetiology and may vary among patients. Some patients may have a rapid progression whereas others would display a slower progression (as in adults with ILD).

The experts also mentioned that the diagnosis of lung fibrosis on HRCT is more difficult in children than in adults.

The experts highlighted that due to the rarity of the underlying diseases, experience would be different among clinical centres, thus reinforcing the need for a multidisciplinary approach for the diagnosis of fibrosis and subsequent progression/treatment decision.

In detail: CT scan represents the main approach for radiological diagnosis. There are instances however in which it can be difficult to diagnose lung fibrosis in children based on HRCT. In case of disagreement, additional radiologists are consulted in clinical practice to ensure appropriate diagnosis.

Some experts mentioned that presence of honeycombing and traction bronchiectasis would mean that there is presence of fibrosis rather than in case of interlobular septal thickening. Honeycombing is seen more often in childhood ILD in older children and represents a later phase with destruction of the lung parenchyma. Presence of ground glass opacities were considered to be less confirmative signs of fibrosis. Furthermore, ground glass opacities can be either fibrotic or inflammatory, and their discrimination is not possible based on HRCT. Ground glass opacities are usually more present in Non-Specific Interstitial Pneumonia (NISP).

If radiology is inconclusive a biopsy may be recommended, depending on the child's clinical status/risk calculation. The experts noted that, depending on the location where the biopsy is performed, important information may be missed, (in case of patchy lesions for example), therefore additional information such as HRCT and clinical manifestations are important to validate the diagnosis of both lung fibrosis and its progression.

The patient representative mentioned the importance of the access to healthcare, early diagnosis and the impact of the environmental factors in children with progressive ILD.

Question 2

The Experts are invited to discuss whether the broad spectrum of fibrosing childhood interstitial lung diseases exhibit sufficient pathophysiologic similarities to conditions for which nintedanib is currently authorised in adults to allow for (full) extrapolation of efficacy from adults to children. Should relevant dissimilarities exist, please consider whether it is possible to identify a subset of fibrosing childhood interstitial lung diseases where such extrapolation could be justified.

The Experts overall agreed that they can accept some dissimilarity in the disease. It was noted that the natural history of most fibrosing entities is not yet clear in the childhood population. Also, in the adult population interindividual differences are seen in start and progression of fibrosis (between different ILD diagnosis and also within the same ILD diagnosis).

The Experts discussed the current indications approved for Ofev in adults: They agreed that the diagnosis idiopathic pulmonary fibrosis (IPF) as such only exists in the adult population. Therefore, for this subset it is not possible to extrapolate. The other 2 indications in the adult population (Other ILD progressive and SSc ILD) can be extrapolated to the childhood population.

They noted that the subset of paediatric patients with auto immune and connective tissue disorders related ILD and SSc-induced ILD have the same pathophysiology as the adult subset.

Overall, the experts agreed that, except from IPF which is not seen in children, the spectrum of fibrosing childhood interstitial lung diseases can be considered to exhibit sufficient pathophysiological similarities in terms of fibrosis development to allow for extrapolation of efficacy from adults to children.

Question 3

The Experts are invited to discuss whether pulmonary fibrosis with a progressive phenotype can be reliably identified in the paediatric population. What is your opinion of the relevance of the criteria used in study 1199-0337 to diagnose pulmonary fibrosis and identify progressive disease in this population?

Summary : All experts agreed that the criteria used in the study 1199-0337 were overall acceptable. The criteria used in the study were as follows: determination of fibrosing ILD on HRCT by the investigator. Clinically significant disease was defined as Fan Score >=3 and evidence of clinical progression. Worsening of fibrosis on HRCT is included as evidence of clinical progression. Central review confirmation was based on pre-defined imaging criteria. For patients with previous pathological findings of fibrosis on lung biopsy, fibrosis on HRCT was confirmed if at least one of the following imaging criteria had been met within 12 months based on central review: reticular abnormality, traction bronchiectasis, architectural distortion, or honeycombing. For patients without any documented lung biopsy or whose biopsy results did not meet the biopsy criteria for fibrosis at least 2 of the following imaging findings were required on at least 2 HRCT scans: reticular abnormality, traction bronchiectasis, architectural distortion with/without ground glass opacification, honeycombing, cystic abnormality.

The experts commented that this approach follows the common approach in the clinic, and it was noted that in some instances a third radiological review may be asked in case of disagreement on the fibrosis and its progression.

However, the experts agreed that for NSIP, the criteria used in study 1199-0337, should have been more restricted to include only fibrosing NSIP. They mentioned also that cellular NSIP will lead to ground glass opacities which does not per se lead to fibrosis.

The experts emphasised again the need for a multidisciplinary approach for the fibrosis diagnosis and evidence of progression. It is important to assess criteria based on pathology and radiology in addition to the clinical feature (fan score and lung function) to make a sound and informed diagnosis.

The timelines to assess clinical progression in Childhood ILD was discussed among experts. It was agreed that the time to perform a second evaluation to ascertain progression may vary depending on underlying aetiologies and the specific case. The experts agreed that a timeframe between 6 to 12 months would be reasonable to ascertain progression and to initiate antifibrotic treatment.

In detail: The Experts noted that study 1199-0337also included non-ILD conditions such as post infection bronchiolitis obliterans. These patients should not have been included.

It was noted that in adults there are tools to quantify the radiological abnormalities and objectively quantify the progression of the disease. However, at present such tools do not exist for Childhood ILD.

In conclusion the CHMP considered the following aspects to conclude on the extrapolation and efficacy of nindetanib in the paediatric population:

Pathophysiologic similarities

Justification for the use of an antifibrotic agent in children, as presented by the MAH, is based on the claim that irrespective of the underlying cause and trigger of the lung injury, pathophysiology of fibrotic remodeling is similar in all fibrosing ILDs irrespective of the age of onset. As stated by Chua et al (2005): “lungs from children with pulmonary fibrosis display many histological features of the adult condition, including increased numbers of interstitial fibroblasts/myofibroblasts, type II alveolar epithelial cell hyperplasia, and varying degrees of background inflammation”. However, despite these similarities differences in pathophysiological pathways of pulmonary fibrosis in children and adults have also been noted (Nathan et al, 2019). At the cellular level fibrosis in children is associated “with more inflammatory cell recruitment and less fibroblast recruitment and ECM deposition”. At the tissue level, the UIP pattern (radiological and histopathological), which is hallmark of IPF and is associated with the highest degree of fibrosis in tissue, is exceptionally or never observed in childhood.

Therefore, extrapolation of efficacy from diseases presenting with UIP pattern (such as IPF) is not considered justified. This opinion was also expressed by the experts at the AHEG meeting.

On the other hand, in fibrosing ILDs in children other patterns have been observed.

In a large study by Rice et al (2013), who reviewed the lung biopsies of 211 patients with various forms of child ILD, a pulmonary fibrosis pattern was found in only 2% of the 93 patients aged under 2 years and in 7% of the 118 patients aged 2–18 years. NSIP was the most prevalent histologic pattern, but the authors highlighted that most pediatric patients harbour coexisting histologic patterns of ILD within the same sample, such as alveolar proteinosis, desquamative interstitial pneumonia (DIP), or follicular bronchiolitis. The experts at the AHEG meeting also indicated that fibrotic NSIP pattern is the most likely to be seen in children with fibrotic ILDs.

Therefore, extrapolation from adult diseases presenting with other fibrosing patterns (such as fibrotic NSIP) could be justified.

It is important to note that based on results of the INBUILD study, fibrotic pattern is very likely to have the impact on the efficacy. In this study absolute and relative difference in comparison to placebo was higher in patients with UIP-like pattern (which have the highest amount of fibrosis) than in patients with other fibrotic patterns.

The treatment effect in children is likely to be similar or smaller (due to less fibroblast recruitment and ECM deposition) than that reported in adult patients with systemic sclerosis associated interstitial lung disease or chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype with other fibrosing pattern treated with nintedanib. Therefore, there is greater uncertainty regarding the magnitude of the treatment effect in children than in adults. This uncertainty is highlighted in section 4.4 of the SmPC.

Extrapolation at disease/indication level

Ofev is currently approved for three adult indications: Idiopathic pulmonary fibrosis (IPF), Systemic sclerosis associated interstitial lung disease (SSc-ILD) and chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.

As discussed, idiopathic pulmonary fibrosis is not being diagnosed in children and therefore extrapolation from this disease is not considered justified. This was also supported by the AHEG experts.

Systemic sclerosis associated interstitial lung disease (SSc-ILD) is diagnosed in both adults and children.

As in adults with SSc, juvenile Systemic Sclerosis (jSSc) is a rare autoimmune connective tissue disease characterized by vascular damage, inflammatory dysregulation, and multiple organ fibrosis. An estimated incidence rate is 0.27-2.9 per million children person-years (<16 years old) and prevalence rate is 3.29 per million children (<16 years old). Disease progression is heterogeneous, with survival for patients with jSSc estimated to be 89.0%- 95% at five years, 87.4% at 10 years, and 82.5% at 20 years after diagnosis. jSSc and adult SSc patients typically present with cutaneous manifestations: edematous, induration, and atrophy. Raynauds Phenonemon (RP), Digital Ulcers (DU), and nailfold capillary changes are all common clinical vasculopathy manifestations (50-90%) of both patients with jSSc and adult SSc. Pulmonary fibrosis is common in all systemic sclerosis (juvenile and adult). In children and adolescents autopsy findings show up to 95% of pulmonary involvement but only up to 39% radiographic findings. Findings on HRCT mirror the histopathologic findings, with the predominant pathologic pattern being an interstitial process similar to nonspecific interstitial pneumonia (NSIP).

The inPedILD study enrolled children with a spectrum of interstitial diseases, including those with SSc-associated ILD. Children with SSc-associated ILD were the second most common subgroup of patients enrolled to the InPedILD study (accounting for 7 (17.9%) children enrolled).

In conclusion, based on pathophysiologic similarities and similarity of the SSc-ILD disease between adults and children, it is agreed to extrapolate data from adult population . This extrapolation combined with the data provided from PedILD in children, supports recommendation of an indication in the paediatric population aged 6 to 17th years. The new indication will be as follows :Ofev is indicated in adults, adolescents and children aged 6 years and older for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD). This approach was also supported by the AHEG.

Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (PF-ILDs)

Nintedanib cannot revert already established fibrosis, but it can slow its progression. Therefore, in adults nintedanib is approved only for diseases with self-sustained, progressive fibrosis, such as in patients with progressive pulmonary fibrosis phenotype.

The INBUILD study, performed in adult patients to support PF-ILD indication, enrolled patients with clinical diagnosis of a chronic fibrosing ILD with greater than 10% fibrotic features on HRCT and presented with clinical signs of progression.

Therefore, there is uncertainty whether the treatment benefits as established in the INBUILD study (in progressive fibrosing phenotype adult population) can be extrapolated to a broad paediatric population as proposed by the MAH, which may also include children without progressive fibrosis.

As highlighted during the AHEG meeting, there is a group of children with fibrosing ILDs which may not progress and/or who could respond to the standard therapies. These patients are not considered as appropriate candidates for nintedanib treatment. On the other hand, the use of nintedanib in children with progressive fibrosis (i.e. not responding to standard therapies) could be justified.

Therefore, upon request by CHMP, the proposed indication was updated as follows: *Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs) (see section 4.2 and 5.1).* This approach was also supported by the AHEG.

- Although, the use in children with clinically significant, progressive fibrosing interstitial lung diseases (ILDs) is justified, additional concerns were required to be addressed by the MAH to ensure appropriate use of the product: There are more than 200 very rare different diseases included under a broad term “childhood ILDs”. Only a small proportion of children with childhood ILD (around 5%) develop clinically significant progressive lung fibrosis. Further, there are no widely accepted radiologic or histopathologic criteria for identification of children with lung fibrosis and as well as for identification of progressive fibrosing phenotype in children. Therefore, there is a concern that due to diagnostic errors or unfamiliarity of physicians, children without progressive fibrosis could be treated with nintedanib. Of note, members of the AHEG strongly highlighted the need for a multidisciplinary team to be involved in the diagnosis and initiation of nintedanib treatment in children with fibrosing ILDs. This recommendation is addressed by including a statement regarding the need of the multidisciplinary team in section 4.2 of the SmPC.
- There is greater uncertainty regarding the magnitude of the treatment benefit in paediatric patients than in adults and this is highlighted in section 4.4 of the SmPC.
- The SmPC also highlights that the data on the use of nintedanib in paediatric patients is limited to a small subset of fibrosing interstitial lung diseases. This subset does not cover all

aetiologies associated with progressive fibrosing interstitial lung disease in paediatric patients. The list of fibrosing interstitial lung diseases is included in section 5.1 of the SmPC.

As limited data across the range of childhood interstitial lung diseases are available, the MAH committed to conduct post-authorisation data collection (LEG) on the use of nintedanib in children in the paediatric population, e.g. through an appropriate EU registry (as currently done for the adult population with systemic sclerosis associated ILD and chronic fibrosing ILD with a progressive phenotype), particularly to describe the patient characteristics and the natural history of diseases not investigated in nintedanib studies or those represented in studies by one patient only. Of note, taking into consideration the rarity of these diseases it is not expected from the MAH to formally compare the treatment effect between nintedanib users and non-users.

2.6.6. Conclusions on clinical efficacy

The efficacy in paediatric patients (6 to 17th years old) with systemic sclerosis associated interstitial lung disease (SSc-ILD or with chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (PF-ILDs) is considered sufficiently demonstrated.

2.6.7. Clinical safety

Two data lock points were put in place DBL1 (17 Feb 2022) and DBL2 (31 May 2023) as previously mentioned.

2.6.7.1. Patient exposure

Extent of exposure in trials 1199-0337 and 1199-0378 (pooled)

During the nintedanib-exposure period (comprising the time from first to last nintedanib administration in each patient) in trial 1199-0337, the mean (SD) duration of exposure to nintedanib overall was 42.1 (22.2) and the median (range) duration of exposure to nintedanib was 41.1 (2.1, 85.1) weeks. At the snapshot date for the pooled analysis of trials 1199-0337 and 1199-0378, the mean (SD) duration of exposure to nintedanib for all patients was 70.0 (41.5) weeks; the median (range) was 78.4 (0.3, 138.4) weeks. In the pooled analysis of trials 1199-0337 and 1199-0378, most patients were treated with nintedanib for more than 76 weeks, with 15 (31.3%) on nintedanib for more than 100 weeks.

Table 46: Nintedanib exposure during the nintedanib-exposure period of trial 1199-0337 alone and of trials 1199-0337 and 1199-0378 (pooled) – TS

	Trial 1199-0337	Trials 1199-0337 and 1199-0378 (pooled)
	Total	Total
Number of patients (N, %)	37 (100.0)	48 (100.0)
Duration of exposure [weeks]		
Mean (SD)	42.1 (22.2)	70.0 (41.5)
Median	41.1	78.4
Minimum, maximum	2.1, 85.1	0.3, 138.4
Duration of exposure in categories [weeks] (N, %)		
≤6	1 (2.7)	3 (6.3)
>6 to ≤24	8 (21.6)	7 (14.6)
>24 to ≤52	13 (35.1)	6 (12.5)
>52 to ≤76	13 (35.1)	7 (14.6)
>76	2 (5.4)	25 (52.1)
Total exposure[1] [patient-years]	29.8	64.4

Treatment interruptions were not subtracted from the duration of exposure.

1 The total exposure [patient-years] is defined as the sum of duration of exposure of all patients [days]/365.25.

2.6.7.2. Adverse events

Trial 1199 0337

The proportion of patients with AEs considered drug-related was slightly higher in the nintedanib group than in the placebo group. AEs leading to discontinuation of trial medication, severe AEs, and SAEs were reported at low frequency only in the nintedanib group and not in the placebo group. The higher frequency of patients with AEs in the nintedanib group was mostly due to infections and gastrointestinal AEs, mainly diarrhoea.

Based on data up to DBL2, the frequencies of patients with AEs and SAEs during the double-blind period in both treatment groups were identical (AEs: 84.6%, SAEs: 7.7%). One more AE leading to treatment discontinuation was reported during the double-blind period based on data up to DBL2.

Table 47: Overall summary of AEs during the double-blind period and over the whole trial (up to DBL2) – TS

	Double-blind period				Whole trial			
	Placebo		Nintedanib		Placebo/ nintedanib		Nintedanib/ nintedanib	
	N	%	N	%	N	%	N	%
Number of patients	13	100.0	26	100.0	13	100.0	26	100.0
Patients with any AE	11	84.6	22	84.6	12	92.3	26	100.0
Patients with severe AEs	0	0	2	7.7	1	7.7	5	19.2
Patients with investigator defined drug-related AEs	5	38.5	14	53.8	7	53.8	18	69.2
Patients with AEs leading to discontinuation of trial medication[1]	0	0	2	7.7	0	0	2	7.7
Patients with AEs of special interest[2]	2	15.4	2	7.7	3	23.1	9	34.6
Patients with SAEs[3]	1	7.7	2	7.7	3	23.1	5	19.2
Results in death	0	0	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0	0
Persistent or significant disability/incapacity	0	0	0	0	0	0	0	0
Requiring or prolonging hospitalisation	0	0	2	7.7	0	0	3	11.5
Congenital anomaly or birth defect	0	0	0	0	0	0	0	0
Other medically important serious event	1	7.7	0	0	3	23.1	2	7.7
Patients with other significant AEs[4]	0	0	4	15.4	1	7.7	4	15.4

Trials 1199-0337 and 1199-0378 (pooled)

Table 48: Overall summary of AEs – TS

	Total	
	N	%
Number of patients	54	100.0
Patients with any AE	53	98.1
Patients with severe AEs	13	24.1
Patients with investigator defined drug-related AEs	39	72.2
Patients with AEs leading to discontinuation of trial medication[1]	3	5.6
Patients with AEs of special interest[2]	12	22.2
Patients with SAEs[3]	15	27.8
Resulting in death	0	0.0
Life-threatening	1	1.9
Persistent or significant disability/incapacity	0	0.0
Requiring or prolonging hospitalisation	10	18.5
Congenital anomaly or birth defect	0	0.0
Other medically important serious event	7	13.0
Patients with other significant AEs[4]	13	24.1

1 Treatment discontinuations were premature and permanent.

2 Protocol-specified AEs of special interest included pathological findings on epiphyseal growth plates on imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, and hepatic injury.

3 A patient could be counted in more than 1 seriousness criterion.

4 Non-serious AEs that led to dose reduction or premature discontinuation of trial medication.

Most frequently reported treatment-emergent adverse events

Double-blind period

DBL1

Based on data up to DBL1, the most frequently reported treatment-emergent AEs in the double-blind period (i.e. the first 24 weeks of treatment) in both treatment groups belonged to the SOC 'gastrointestinal disorders'. The proportion of patients with diarrhoea was higher in the nintedanib group (30.8%) than in the placebo group (7.7%), whereas the proportion of patients with vomiting and nausea was in general comparable between the treatment groups. The proportion of patients with dental caries was slightly higher in the nintedanib group (23.1%) than in the placebo group (15.4%). Infections and infestations were reported more frequently in the nintedanib group (38.5%) than in the placebo group (15.4%).

The frequency of respiratory, thoracic and mediastinal disorders was lower (7.7%) in the nintedanib group than in the placebo group (30.8%). Within the SOC ‘infections and infestations’ AEs of COVID-19 and rhinitis were reported only in the nintedanib group and not in the placebo group.

DBL2

Like in the double-blind period up to DBL1, the most frequently reported AEs during the double-blind period up to DBL2 belonged to the SOC ‘gastrointestinal disorders’, with diarrhoea being the most frequently reported PT in the nintedanib group. The frequency of dental caries was similar in the nintedanib group (26.9%) and the placebo group (23.1%). Based on data up to DBL2, the frequency of patients with infections and infestations increased in the placebo group (23.1%) and not in the nintedanib group (38.5%). This was driven by 1 patient reported with COVID-19 in the placebo group during the double-blind period based on data up DBL2.

Table 49: AEs reported for more than 10% of patients in either treatment group on the PT level during the double-blind period (up to DBL2) – TS

System organ class Preferred term	Placebo		Nintedanib	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	13 (100.0)		26 (100.0)	
Patients with any AE	11 (84.6)	877.2	22 (84.6)	840.5
Gastrointestinal disorders	11 (84.6)	555.7	22 (84.6)	683.3
Diarrhoea	2 (15.4)	35.6	10 (38.5)	129.1
Dental caries	3 (23.1)	65.2	7 (26.9)	85.1
Vomiting	3 (23.1)	65.2	7 (26.9)	76.3
Abdominal pain	3 (23.1)	61.0	5 (19.2)	51.5
Nausea	3 (23.1)	60.2	5 (19.2)	53.5
Tooth impacted	2 (15.4)	41.8	2 (7.7)	19.1
Faeces soft	2 (15.4)	41.3	1 (3.8)	9.0
Infections and infestations	3 (23.1)	59.7	10 (38.5)	107.7
COVID-19	1 (7.7)	17.8	5 (19.2)	46.8
Rhinitis	0	0	3 (11.5)	28.8
General disorders and administration site conditions	3 (23.1)	63.9	8 (30.8)	85.8
Fatigue	2 (15.4)	40.5	2 (7.7)	19.1
Pyrexia	1 (7.7)	19.1	3 (11.5)	27.9
Respiratory, thoracic and mediastinal disorders	4 (30.8)	81.9	4 (15.4)	36.2
Oropharyngeal pain	2 (15.4)	35.4	1 (3.8)	8.9
Epistaxis	2 (15.4)	40.5	0	0
Nervous system disorders	3 (23.1)	62.4	3 (11.5)	28.8
Headache	1 (7.7)	19.1	3 (11.5)	28.8
Investigations	3 (23.1)	64.3	2 (7.7)	18.9
X-ray limb abnormal	2 (15.4)	39.4	0	0

pt-yrs: patient-years

Incidence rates were calculated using the number of patients with respective events per treatment divided by time at risk expressed as 100 pt-yrs.

Trials 1199-0337 and 1199-0378 (pooled)

The most frequently reported treatment-emergent AEs belonged to the system organ class (SOC) ‘gastrointestinal disorders’, followed by ‘infections and infestations’.The most common PTs were diarrhoea, vomiting, abdominal pain, nausea, and dental caries.

Table 50: AEs reported for more than 10% of patients at the PT level – TS

System organ class PT	Total N (%)	 Rate/100 pt-yrs
Number of patients	54 (100.0)	-
Patients with any AE	53 (98.1)	932.93
Gastrointestinal disorders	48 (88.9)	400.64
Diarrhoea	28 (51.9)	74.73
Vomiting	20 (37.0)	41.44
Abdominal pain	16 (29.6)	28.40
Nausea	16 (29.6)	32.69
Dental caries	15 (27.8)	29.61
Tooth development disorder	7 (13.0)	12.16
Infections and infestations	35 (64.8)	115.03
COVID-19	13 (24.1)	24.51
Upper respiratory tract infection	7 (13.0)	11.00
Rhinitis	6 (11.1)	9.50
Respiratory, thoracic and mediastinal disorders	26 (48.1)	52.88
Cough	8 (14.8)	12.76
General disorders and administration site conditions	20 (37.0)	39.80
Pyrexia	9 (16.7)	14.74
Chest pain	6 (11.1)	9.43
Investigations	19 (35.2)	34.89
Weight decreased	6 (11.1)	9.27
Nervous system disorders	10 (18.5)	16.67
Headache	10 (18.5)	16.67

pt-yrs: patient-years.

Incidence rates were calculated using number of patients with the respective events divided by time at risk expressed per 100 pt-yrs

Severe adverse events

Double-blind period

Based on data up to DBL1, during the double-blind period severe AEs were reported for 2 (7.7%) patients in the nintedanib group. This comprised 1 patient with a severe AE of COVID-19 and 1 patient with severe increased carbon dioxide and severe respiratory distress.

Severe AEs in one patient were reported during an off-treatment period (onset of AEs was 43 days after the start of treatment interruption). None of the patients in the placebo group were reported with severe AEs up to DBL1.

Compared with the data up to DBL1, no additional severe AEs were reported during the double-blind period based on data up to DBL2.

Trials 1199-0337 and 1199-0378 (pooled)

Over the nintedanib exposure period of both trials, severe AEs were reported for 13 (24.1%) patients. The only PTs reported in more than 1 patient were COVID-19, interstitial lung disease, and tooth development disorder.

Table 51: Severe AEs – TS

System organ class	Total	
PT	N (%)	Rate/100 pt-yrs
Number of patients	54 (100.0)	
Patients with at least 1 severe AE	13 (24.1)	22.39
Respiratory, thoracic and mediastinal disorders	7 (13.0)	10.39
Interstitial lung disease	2 (3.7)	2.92
Dyspnoea	1 (1.9)	1.44
Pneumothorax	1 (1.9)	1.44
Pulmonary hypertension	1 (1.9)	1.44
Respiratory distress	1 (1.9)	1.44
Respiratory failure	1 (1.9)	1.43
Infections and infestations	3 (5.6)	4.52
COVID-19	2 (3.7)	3.01
Respiratory tract infection	1 (1.9)	1.43
Gastrointestinal disorders	3 (5.6)	4.59
Tooth development disorder	2 (3.7)	3.02
Abdominal pain	1 (1.9)	1.45
Investigations	2 (3.7)	2.87
Carbon dioxide increased	1 (1.9)	1.44
Weight decreased	1 (1.9)	1.43
Blood and lymphatic system disorders	1 (1.9)	1.44
Sickle cell anaemia with crisis	1 (1.9)	1.44
Hepatobiliary disorders	1 (1.9)	1.45
Hepatitis	1 (1.9)	1.45
Congenital, familial and genetic disorders	1 (1.9)	1.43
Sickle cell anaemia	1 (1.9)	1.43
Injury, poisoning and procedural complications	1 (1.9)	1.46
Ligament sprain	1 (1.9)	1.46

pt-yrs: patient-years.

Incidence rates were calculated using number of patients with the respective events divided by time at risk expressed per 100 pt-yrs

Investigator-defined drug-related AEs

Double-blind period

In the double-blind period up to DBL1, the proportion of patients with AEs which were considered drug-related by the investigator was slightly higher in the nintedanib group (46.2%) than in the placebo group (38.5%;). The most frequently reported drug-related AEs were in the SOC 'gastrointestinal disorders' (nintedanib: 38.5%, placebo: 30.8%). The most frequent PTs overall (reported for >3 patients in total) were diarrhoea (nintedanib: 19.2%, placebo: 7.7%), nausea (nintedanib: 11.5%, placebo: 7.7%), vomiting (nintedanib: 11.5%, placebo: 7.7%), and abdominal pain (nintedanib: 15.4%, placebo: 0%).

Drug-related AEs in other SOCs were reported by 3 patients overall or less.

Table 52: Investigator-defined drug-related AEs during the double-blind period (up to DBL1) – TS

System organ class Preferred term	Placebo		Nintedanib	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	13 (100.0)		26 (100.0)	
Patients with any drug-related AE	5 (38.5)	127.4	12 (46.2)	164.3
Gastrointestinal disorders	4 (30.8)	101.6	10 (38.5)	123.6
Diarrhoea	1 (7.7)	19.5	5 (19.2)	56.2
Nausea	1 (7.7)	21.1	3 (11.5)	31.9
Vomiting	1 (7.7)	21.1	3 (11.5)	31.0
Abdominal pain	0	0	4 (15.4)	42.3
Abdominal pain upper	0	0	2 (7.7)	20.3
Faeces soft	1 (7.7)	21.2	1 (3.8)	9.7
Constipation	1 (7.7)	20.6	0	0
Lower gastrointestinal haemorrhage	0	0	1 (3.8)	9.5
General disorders and administration site conditions	1 (7.7)	20.6	2 (7.7)	20.6
Fatigue	1 (7.7)	20.6	2 (7.7)	20.6
Chest pain	0	0	1 (3.8)	9.8
Musculoskeletal and connective tissue disorders	1 (7.7)	19.4	2 (7.7)	19.9
Back pain	0	0	1 (3.8)	9.8
Epiphyses premature fusion	0	0	1 (3.8)	9.6
Arthralgia	1 (7.7)	19.4	0	0
Metabolism and nutrition disorders	1 (7.7)	20.6	1 (3.8)	9.9
Decreased appetite	0	0	1 (3.8)	9.9
Dehydration	0	0	1 (3.8)	9.8
Increased appetite	1 (7.7)	20.6	0	0
Vascular disorders	0	0	1 (3.8)	9.9
Hot flush	0	0	1 (3.8)	9.9
Psychiatric disorders	0	0	1 (3.8)	9.8
Insomnia	0	0	1 (3.8)	9.8
Nervous system disorders	0	0	1 (3.8)	9.8
Headache	0	0	1 (3.8)	9.8
Investigations	0	0	1 (3.8)	9.8
Liver function test increased	0	0	1 (3.8)	9.8

The profile of investigator-defined drug-related AEs on the PT level reported during the double-blind period up to DBL2 was generally consistent with the profile of drug-related AEs reported during the double-blind period up to DBL1. The most frequently reported drug-related AEs were in the SOC 'gastrointestinal disorders' (nintedanib: 46.2%, placebo: 30.8%) and mainly included diarrhoea (nintedanib: 26.9%, placebo: 7.7%), abdominal pain (nintedanib: 19.2%, placebo: 0%), vomiting (nintedanib: 15.4%, placebo: 7.7%), and nausea (nintedanib: 11.5%, placebo: 7.7%). Based on data up to DBL2, 1 (3.8%) drug-related liver injury was reported in the nintedanib group whereas no hepatobiliary disorders were reported in the placebo group (0%) during the double-blind period.

Trials 1199-0337 and 1199-0378 (pooled)

Over the nintedanib exposure period of both trials, drug-related AEs as defined by the investigator were reported for 39 (72.2%) patients. Table 53 shows drug-related AEs that were reported for more than 1 patient (i.e. more than 3% of patients).

Two-thirds of these AEs belonged to the SOC ‘gastrointestinal disorders’. On PT level, the most frequent drug-related AEs (reported in >10 patients) were diarrhoea, vomiting, abdominal pain, and nausea.

Table 53: Investigator-defined drug-related AEs reported for more than 3% of patients at the PT level – TS

System organ class	Total	
PT	N (%)	Rate/100 pt-yrs
Number of patients	54 (100.0)	-
Patients with at least 1 drug-related AE	39 (72.2)	130.10
Gastrointestinal disorders	36 (66.7)	112.46
Diarrhoea	22 (40.7)	46.00
Vomiting	14 (25.9)	23.81
Abdominal pain	13 (24.1)	21.37
Nausea	13 (24.1)	24.23
Abdominal pain upper	4 (7.4)	6.09
Tooth development disorder	4 (7.4)	6.37
Investigations	9 (16.7)	14.25
Weight decreased	4 (7.4)	6.04
Hepatic enzyme increased	2 (3.7)	2.95
General disorders and administration site conditions	5 (9.3)	8.01
Chest pain	3 (5.6)	4.60
Fatigue	3 (5.6)	4.58
Hepatobiliary disorders	5 (9.3)	7.58
Liver injury	2 (3.7)	2.94
Psychiatric disorders	4 (7.4)	5.81
Anxiety	2 (3.7)	2.88
Metabolism and nutrition disorders	3 (5.6)	4.47
Decreased appetite	2 (3.7)	2.95
Nervous system disorders	3 (5.6)	4.46
Headache	3 (5.6)	4.46

AEs of special interest

Gastrointestinal and metabolic safety topics

Double-blind period

Based on data up to DBL1, the most common AEs in the gastrointestinal or metabolic organ system on the safety topic level were dental disorders, vomiting, diarrhoea, abdominal pain, and nausea. Within gastrointestinal safety topics, the only safety topic for which the proportion of patients with AEs was higher in the nintedanib group than in the placebo group was diarrhoea. Within metabolic safety topics, only 1 AE was reported. This comprised 1 (3.8%) patient receiving nintedanib reported with decreased appetite. No SAEs were reported in the gastrointestinal or metabolic organ system.

The profile of AEs reported in gastrointestinal and metabolic safety topics during the double-blind period up to DBL2 was generally consistent with the profile of AEs in gastrointestinal and metabolic safety topics reported during the double-blind period up to DBL1 with no relevant changes in incidence rates observed.

Table 54: AEs and SAEs by gastrointestinal and metabolic safety topics during the double-blind period (up to DBL2) – TS

Organ system/ *Safety topic*		Placebo N (%)	Rate/ 100 pt-yrs	Nintedanib N (%)	Rate/ 100 pt-yrs
Number of patients		13 (100.0)		26 (100.0)	
Gastrointestinal AEs	**Patients with**				
Dental disorders[1,2]	any AE	7 (53.8)	248.7	9 (34.6)	118.8
	SAE	0	0	0	0
Vomiting[3]	any AE	3 (23.1)	65.2	7 (26.9)	76.3
	SAE	0	0	0	0
Diarrhoea[3]	any AE	2 (15.4)	35.6	10 (38.5)	129.1
	SAE	0	0	0	0
Abdominal pain[1]	any AE	4 (30.8)	88.6	6 (23.1)	64.3
	SAE	0	0	0	0
Nausea[3]	any AE	3 (23.1)	60.2	5 (19.2)	53.5
	SAE	0	0	0	0
Tooth developmental disorders[1,4,5]	any AE	4 (30.8)	96.4	3 (11.5)	30.0
	SAE	0	0	0	0
Metabolic AEs	**Patients with**				
Decreased appetite[3]	any AE	0	0	1 (3.8)	9.2
	SAE	0	0	0	0

pt-yrs: patient-years

Diarrhoea

Double-blind period

During the double-blind period up to DBL1, 8 patients receiving nintedanib and 1 patient receiving placebo had at least 1 diarrhoea AE. Compared with data based on DBL1, 2 additional patients in the nintedanib group and 1 additional patient in the placebo group were reported with diarrhoea (CTCAE grade 1 or 2) during the double-blind period up to DBL2. None of the reported diarrhoea AEs led to premature discontinuation of trial medication. For most patients with diarrhoea AEs in the nintedanib group, the AEs were assessed as drug-related by the investigator.

In the nintedanib group, most patients w had their first diarrhoea episode in the first 2 weeks of treatment.

Trials 1199-0337 and 1199-0378 (pooled)

AEs by safety topic

On PT level, the most common AEs (>10 patients) within gastrointestinal safety topics were diarrhoea (28 patients, 51.95%), vomiting (20 patients, 37.0%), abdominal pain (16 patients, 29.6%; contained in safety topic 'abdominal pain'), nausea (16 patients, 29.6%), and dental caries (15 patients, 27.8%; contained in 'dental disorders'). Within metabolic safety topics, the PTs decreased appetite (3 patients, 5.6%) and weight decreased (6 patients, 11.1%) were reported.

SAEs within gastrointestinal safety topics included abdominal pain and tooth development disorder (contained in both dental disorders and tooth developmental disorders). No metabolic SAEs were reported.

Table 55: AEs and SAEs by gastrointestinal and metabolic safety topics – TS

Organ system		Total	
Safety topic	Patients with	N (%)	Rate/100 pt-yrs
Number of patients			
Gastrointestinal AEs			
Diarrhoea[1]	any AE	28 (51.9)	74.73
	SAE	0	0
Dental disorders[2,3]	any AE	22 (40.7)	55.86
	SAE	1 (1.9)	1.47
Vomiting[1]	any AE	20 (37.0)	41.44
	SAE	0	0
Abdominal pain[2]	any AE	18 (33.3)	33.43
	SAE	1 (1.9)	1.45
Nausea[1]	any AE	16 (29.6)	32.69
	SAE	0	0
Tooth developmental disorders[2,4]	any AE	8 (14.8)	14.31
	SAE	1 (1.9)	1.47
Metabolic AEs		0	0
Weight decreased[1]	any AE	6 (11.1)	9.27
	SAE	0	0
Decreased appetite[1]	any AE	3 (5.6)	4.43
	SAE	0	0

pt-yrs: patient-years. An AE could be displayed in more than 1 safety topic.

AESIs related to gastrointestinal perforation and to dental imaging/examination

No gastrointestinal perforation was reported over the nintedanib exposure period of both trials

Dental disorders

Of note, pathological findings from dental imaging or examination identified at the baseline assessment (performed up to Day 15, but after start of treatment) were also considered on-treatment AEs if reported on the AE page by the investigator ever, it is not expected that nintedanib treatment would lead to changes of the teeth within the first 2 weeks of treatment.

In the safety topic 'dental disorders' the AEs of 9 patients in the nintedanib group and 6 patients in the placebo group were identified at the baseline assessment. Likewise, in the safety topic 'tooth developmental disorders' the AEs of 3 patients in the placebo group were identified at the baseline assessment.

Double-blind period

Two patients in the nintedanib group were subsequently reported with AEs in the safety topic ‘dental disorders’ in the double-blind period up to DBL1 outside of the baseline window. Based on data up to DBL2, 1 more patient was subsequently reported with AEs in the safety topics ‘dental disorders’ and ‘tooth developmental disorders’ in the double-blind period outside of the baseline window.

Trials 1199-0337 and 1199-0378 (pooled)

In the pooled analysis of trials 1199-0337 and 1199-0378, dental-related AEs were reported for 20 (41.7%) patients in the safety topic ‘dental disorders’ and for 8 (16.7%) patients in the safety topic ‘tooth developmental disorders. Please note that out of these patients, 11 (22.9%) were reported with AEs in the safety topics ‘dental disorders’ or ‘tooth developmental disorders’ related to the baseline examination.

Table 56: AEs within safety topics ‘dental disorders’ and ‘tooth developmental disorders’ reported during the nintedanib-exposure period of pooled trials 1199-0337 and 1199-0378 – TS

Patient	Trial period (day) at AE onset[2,3]	Preferred term[4]
Randomised to placebo in trial 1199-0337		
Patient	Open-label (373)	Tooth discolouration
Patient	Open-label (221)	Dental caries
Patient	Baseline (1)	Tooth deposit
	Open-label (96)	Dental caries
Patient	Open-label (114)	Dental caries
		Tooth hypoplasia
Randomised to nintedanib in trial 1199-0337		
Patient	Baseline (1)	Dental caries, tooth fracture, tooth development disorder
	Open-label (362)	Dental caries, malpositioned teeth
Patient	Baseline (1)	Dental caries
Patient	Baseline (1)	Dental caries, tooth impacted
	Open-label (166)	Dental cyst, tooth development disorder
	Open-label (184)	Malpositioned teeth
Patient	Baseline (1)	Dental caries
	Open-label (169, 358, 505, 588)	Dental caries
Patient	Baseline (1)	Tooth abscess, dental caries
	Double-blind (85)	Dental caries
	Open-label (176)	Tooth development disorder
	Open-label (253, 359, 730)	Dental caries
Patient	Baseline (1)	Dental caries
	Double-blind (29)	Dental cyst
	Double-blind (177)	Dental caries
Patient	Baseline (1)	Tooth impacted, tooth development disorder[5]
	Double-blind (85)	Tooth impacted
	Open-label (169)	Tooth development disorder, tooth impacted
Patient	Baseline (1)	Malpositioned teeth, dental plaque, malocclusion
Patient	Open-label (205)	Tooth development disorder
Patient	Open-label (168)	Tooth abscess
Patient	Open-label (165)	Tooth development disorder

Patient	Trial period (day) at AE onset[2,3]	Preferred term[4]
Patient	Open-label (170)	Tooth development disorder
Patient	Baseline (1)	Dental caries
	Open-label (697)	Dental caries
Patient	Open-label (331)	Dental caries
New patients in trial 1199-0378		
Patient	Open-label (84)	Dental caries
Patient	Baseline (4)	Dental caries

A total of 6 (12.5%) patients were reported with AESIs of stunted growth of dental root as documented by the investigator during the nintedanib-exposure period of pooled trials 1199-0337 and 1199-0378 . All the AESIs were reported in trial 1199-0337. In all 6 patients, a corresponding dental examination showed no relevant pathological findings. As per the assessment of the dentist paediatric expert member of the SMC, no relevant differences in the interpretation of radiographic presentation of the teeth were observed on images at baseline and at the follow-up and trial drug had no causal relationship with the dental morphology or development of the teeth root. Continuation of treatment with nintedanib was recommended in all the patients. For 5 out of 6 patients reported with AESIs of stunted growth of dental root, no indication of stunted growth of dental root was reported by the central review based on follow-up dental imaging at Week 52 of nintedanib treatment. For the remaining patient, based on images at Week 52 of nintedanib treatment, pathological findings were described only for 4 of 10 teeth with previously reported stunted growth of dental root Except for a finding of dental caries, all 6 patients had no pathological findings on the dental examination at Week 52 of nintedanib treatment.

No findings of stunted growth of the dental root and no new AESIs of stunted growth of dental root were reported in trial 1199-0378 as presented in the interim analysis . Five of the 6 patients reported with stunted growth of dental root rolled over to the extension trial (1199-0378). In trial 1199-0378 , follow-up dental imaging became available for all 5 patients who rolled over. Except for a finding of dental caries, no other findings on the dental examination were noted for 5 patients with dental examination performed at Week 122 of nintedanib treatment.

Table 57: Description of findings in patients with stunted growth of dental root

Age[1]	Time window of imaging[2]	Pathological finding (tooth affected)[3,4]	SMC paediatric dentist expert evaluation of teeth with stunted growth reported by the central review
14 years	Baseline	Short root (31, 41) Tooth development disorder (ectopic 34 and 44) Impacted permanent teeth (14, 26, 27, 33, 37, 38, 43, 47, 48)	No difference in radiographic presentation of teeth 31 and 41 from baseline to Weeks 24 and 52; root development of teeth 31 and 41 typically completed by the age of 9 years, therefore, the impact of trial medication at the age of 14 is unlikely.
	24 weeks	Stunted growth of dental root (31, 41)	
	52 weeks	No indication of stunted growth of dental root (31, 41)	
12 years	Baseline	Short root (11, 21) Impacted permanent teeth (15, 25, 35)	Tooth 15: no difference in radiographic presentation from baseline to Week 24; some tooth movement possible due to orthodontic treatment; positioning could impact the tooth appearance in the panoramic image
	24 weeks	Stunted growth of dental root (15, 24, 47)	Tooth 24: Although evaluation of root length on the image at Week 24 difficult (overlap with tooth 25), likely no difference in root length from baseline to Week 24; orthodontic treatment could cause tooth movement; positioning could impact the tooth appearance in the panoramic image
	52 weeks	No indication of stunted growth of dental root (15, 24, 47)	Tooth 47: no difference in radiographic presentation from baseline to Week 24
16 years	Baseline	Short root (11, 31, 41) Abscess (37)	No difference in radiographic presentation of tooth 11 from baseline to Week 24
	24 weeks	Stunted growth of dental root (11)	Dental treatment of tooth 11 resulting in large restoration conducted after the baseline imaging could account for the difference in the root appearance compared with baseline.
	52 weeks	No indication of stunted growth of dental root (11)	Root development of tooth 11 typically completed by the age of 9 to 10 years, therefore the impact of trial medication at the age of 16 is unlikely.
6 years	Baseline	Impacted permanent tooth (37)	Image quality from Week 24 insufficient for evaluation of root length; on high-quality radiographic images taken at Week 52 root development normal for teeth 31, 32, 41, and 42
	24 weeks	Stunted growth of dental root (11, 12, 13, 21, 22, 23, 31, 32, 41, 42)	
	52 weeks	Stunted growth of dental root (31, 32, 41, 42)	

Age[1]	Time window of imaging	Pathological finding (tooth affected)[2,3]	SMC paediatric dentist expert evaluation of teeth with stunted growth reported by the central review
15 years	Baseline	No pathological findings	At baseline, ongoing orthodontic treatment with crowding of the maxillary teeth present with teeth 24 and 25 appearing rotated; on image at Week 24, teeth rotated and misaligned, but their position improved compared with baseline; root development of teeth 24 and 25 is typically completed by the age of 12 to 14 years, therefore the impact of trial medication at the age of 15 is unlikely.
	24 weeks	Stunted growth of dental root (24, 25)	
	52 weeks	No indication of stunted growth of dental root (24, 25)	
13 years	Baseline	Short root (11, 21) Impacted permanent teeth (17, 27, 47)	At Week 24 tooth 17 had normal anatomy and morphology surrounding the roots and periodontal tissues; although the appearance of tooth 17 is different than tooth 27, this is most likely due to positioning and the impact of the maxillary sinus on the image; dental development progress is normal.
	24 weeks	Stunted growth of dental root (17)	
	52 weeks	No indication of stunted growth of dental root (17)	

Hepatobiliary and liver laboratory safety topics

Double-blind period

In the double-blind period up to DBL1, 1 AE was reported. The AE of increased liver function test on the PT level was reported in the patient receiving nintedanib, based on elevated liver function tests. The event resolved while the dose of nintedanib was not changed.

1 additional patient receiving nintedanib reported wan AE in hepatobiliary and liver laboratory safety topics during the double-blind period based on data up to DBL2. This patient had with liver injury which led to discontinuation of treatment with trial medication. This AE was considered an AESI by the investigator.

Table 58: AEs and SAEs by hepatobiliary and liver laboratory safety topics during the double-blind period (up to DBL2) – TS

Organ system *Safety topic* *Subcategory*		Placebo N (%)	Placebo Rate/ 100 pt-yrs	Nintedanib N (%)	Nintedanib Rate/ 100 pt-yrs
Number of patients		13 (100.0)		26 (100.0)	
Hepatobiliary AEs	**Patients with**				
Hepatic disorders combined[1]	any AE	0	0	2 (7.7)	18.3
	SAE	0	0	0	0
Drug-related hepatic disorders[2]	any AE	0	0	2 (7.7)	18.3
	SAE	0	0	0	0
Liver-related investigations, signs and symptoms[2]	any AE	0	0	1 (3.8)	9.1
	SAE	0	0	0	0
Hepatic failure[1]	Any AE	0	0	1 (3.8)	8.9
	SAE	0	0	0	0
Liver laboratory AEs	**Patients with**				
Hepatic enzyme increased[1]	any AE	0	0	1 (3.8)	9.1
	SAE	0	0	0	0

Trials 1199-0337 and 1199-0378 (pooled)

AEs by safety topic

A total of 10 (patients were reported with AEs in the hepatobiliary and liver laboratory organ system during the nintedanib-exposure period of trials 1199-0337 and 1199-0378 pooled.

This comprised 6 patients reported with the AEs in trial 1199-0337: 2 in the double-blind period (for details, see the subsection on trial 1199-0337 above) and 4 during the open-label treatment with nintedanib.

- 1 patient with an SAE of liver injury
- 1 patient (with an SAE of DILI
- 2 patients with AEs of increased hepatic enzyme

SAEs of liver injury and DILI were considered as AESIs by the investigator. For details of these AEs, see 'AESIs with respect to liver injury' subsection below. In the 2 patients with AEs of increased hepatic enzyme, the AEs were reported during the residual effect period and were assessed as drug related by the investigator, non-serious, and mild or moderate in intensity. The highest liver enzyme elevations in these patients were observed for ALT with maximum ALT values of 3.7x ULN in one patient and of 1.3x ULN in another patient. Of note one patient reported also drug related AE of increased hepatic enzymes of mild intensity in the extension study.

Four additional patients were reported with AEs in the hepatobiliary and liver laboratory organ system in trial 1199-0378). This comprised:

- 1 patient with AEs of increased aspartate aminotransferase (AST) and increased blood alkaline phosphatase (ALKP). Both AEs were drug related, non-serious, and mild in intensity. The highest observed liver enzyme elevations based on the central laboratory evaluation were 1.1x ULN for AST and 1.4x ULN for ALKP The patient was still on treatment at the time of the snapshot.
- 1 patient with an SAE of non-infectious hepatitis which was also documented as an AESI by the investigator
- 1 patient with AEs of increased hepatic enzymes and increased transaminases, which were also documented as AESIs by the investigator
- 1 patient with a drug-related AE of non-infectious hepatitis. The AE was mild in intensity. The event of hepatitis manifested by increase in liver enzymes of 3.2x ULN for ALT and 1.7x ULN for AST. The liver enzymes normalised within 1 week after treatment interruption. Nintedanib was resumed at a decreased dose without recurrence of the event

Most frequently, hepatobiliary and liver laboratory related AEs belonged to the subcategoriesdrug related hepatic disorders (10 patients, 18.5%), liver related investigations, signs and symptoms (5 patients, 9.3%), and to the safety topic hepatic enzyme increased (5 patients, 9.3%).

Table 59: 27 AEs and SAEs by hepatobiliary and liver laboratory safety topics

Organ system Safety topic Subcategory	Patients with	Total N (%)	 Rate/100 pt-yrs
Number of patients		54 (100.0)	-
Hepatobiliary AEs			
Hepatic disorders combined[1]	any AE	10 (18.5)	15.99
	SAE	3 (5.6)	4.55
Drug related hepatic disorders[2]	any AE	10 (18.5)	15.99
	SAE	3 (5.6)	4.55
Liver related investigations, signs and symptoms[2]	any AE	5 (9.3)	7.51
	SAE	0	0
Hepatitis, non-infectious[2]	any AE	2 (3.7)	2.91
	SAE	1 (1.9)	1.45
Cholestasis and jaundice of hepatic origin[2]	any AE	1 (1.9)	1.46
	SAE	1 (1.9)	1.46
Hepatic failure[1]	any AE	3 (5.6)	4.49
	SAE	2 (3.7)	2.99
Drug-induced liver injury[1]	any AE	1 (1.9)	1.46
	SAE	1 (1.9)	1.46
Liver laboratory AEs			
Hepatic enzyme increased[1]	any AE	5 (9.3)	7.51
	SAE	0	0
Aspartate aminotransferase increased[1]	any AE	1 (1.9)	1.45
	SAE	0	0
Blood alkaline phosphatase increased[1]	any AE	1 (1.9)	1.45
	SAE	0	0

Musculoskeletal safety topic

Double-blind period

During the double-blind period up to DBL2, 1 (3.8%) patient in the nintedanib group and 2 (15.4 %) patient in the placebo group were reported with AEs of growth plate disorders.

One patient in the nintedanib group was reported with an AE of premature fusion of epiphyses based on local bone imaging interpretation that suggested a potential premature fusion of the epiphyses. This AE led to trial discontinuation of trial medication. This pathological finding, however, was not confirmed by the central review and the SMC assessment. The status of epiphyseal closure was open (at

Week 12 and in the follow-up at Weeks 24 to 52;). Furthermore, the patient grew 1 cm from Week 0 to Week 12 while on trial medication and continued to grow in the follow-up period (change in standing height of 4 cm over the 65 weeks of the follow-up period.

The pathological finding in 2 patients on placebo were identified at the baseline assessment (performed up to Day 15 after the start of treatment) therefore they are not considered as relevant.

Table 60: AEs and SAEs by musculoskeletal safety topics during the double-blind period (up to DBL2) – TS

Organ system		Placebo		Nintedanib	
Safety topic / Preferred term		N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs
Number of patients		13 (100.0)		26 (100.0)	
Musculoskeletal AEs	**Patients with**				
Growth plate disorders[1,2]	any AE	2 (15.4)	39.4	1 (3.8)	8.9
	SAE	0	0	0	0
X-ray limb abnormal	any AE	2 (15.4)	39.4	0	0
	SAE	0	0	0	0
Epiphyses premature fusion	any AE	0	0	1 (3.8)	8.9
	SAE	0	0	0	0

pt-yrs: patient-years
An AE could be displayed in more than 1 safety topic.
1 Grouping of MedDRA PTs (see Appendix 16.2.7, Listing 4.1)
2 Two patients in the placebo group were reported with AEs of 'x-ray limb abnormal' only at the baseline assessment (performed up to Day 15 but after the start of treatment)

1199-0378 trial

No AEs in musculoskeletal safety topic were reported in trial 1199-0378 up to the interim analysis date.

Bleeding

Double-blind period

There were 2 patients with events of bleeding in the placebo group (reported PTs 'Rectal haemorrhage' [n=1] and 'Epistaxis' [n=2])) and 1 patient in the nintedanib group (reported PT 'Lower gastrointestinal haemorrhage' [n=1]). The reported events of bleeding were nonserious and of mild intensity in both treatment groups.

Trials 1199-0337 and 1199-0378 (pooled)

AEs by safety topic

A total of 7 (14.6%) patients were reported with the AEs in the bleeding safety topic and 4 (8.3%) patients were reported with AEs in the haematological safety topics during the nintedanib-exposure period of trials 1199-0337 and 1199-0378 pooled. Within the bleeding safety topic this comprised in trial 1199-0337:

- 1 patient with lower gastrointestinal bleeding (documented as an AESI by the investigator)
- 1 patient with heavy menstrual bleeding
- 2 patients with epistaxis and in trial 1199-0378
- 1 patient with epistaxis
- 1 patient with haemoptysis (documented as an AESI by the investigator),
- 1 patient with haematuria

In the haematological safety topics, all AEs were reported in trial 1199-0378 and comprised:

- 1 patient with neutropenia and white blood cell count decreased
- 1 patient with neutrophil count decreased
- 1 patient with thrombocytopenia and leukopenia

- 1 patient with thrombocytopenia
- 1 patient with leukopenia

Except 1 ongoing (at the time of the snapshot) episode of neutropenia, all bleeding and haematological AEs during the nintedanib exposure period had resolved at the time of the snapshot for the pooled analysis without premature treatment discontinuation or dose reduction of trial medication.

No SAEs were reported in the bleeding and haematological safety topics during the nintedanib-exposure period of trials 1199-0337 and 1199-0378 pooled.

Table 61: AEs and SAEs by bleeding and haematological safety topics during the nintedanib-exposure periods in trial 1199-0337 and pooled trials 1199-0337 and 1199-0378 – TS

Organ system *Safety topic* *Subcategory*		Total in trial 1199-0337		Total in trials 1199-0337 and 1199-0378 (pooled)	
		N (%)	Rate/ 100 pt-yrs	N (%)	Rate/ 100 pt-yrs
Number of patients		37 (100.0)		48 (100.0)	
Blood AEs	Patients with				
Bleeding[1]	any AE	4 (10.8)	13.6	7 (14.6)	12.7
	SAE	0	0	0	0
Respiratory bleeding[2]	any AE	2 (5.4)	6.7	4 (8.3)	6.8
	SAE	0	0	0	0
Urogenital bleeding[2]	any AE	1 (2.7)	3.3	2 (4.2)	3.4
	SAE	0	0	0	0
Gastrointestinal bleeding - lower[2]	any AE	1 (2.7)	3.2	1 (2.1)	1.7
	SAE	0	0	0	0
Neutropenia[1]	any AE	0	0	3 (6.3)	5.0
	SAE	0	0	0	0
Haematopoietic thrombocytopenia[1]	any AE	0	0	2 (4.2)	3.3
	SAE	0	0	0	0
Thrombocytopenia[1]	any AE	0	0	2 (4.2)	3.3
	SAE	0	0	0	0

pt-yrs: patient-years. An AE could be displayed in more than 1 safety topic.

Infection safety topics

Double-blind period

During the double-blind period up to DBL1, 5 (19.2%) patients in the nintedanib group and 1 (7.7%) patient in the placebo group were reported with AEs in infection safety topics. All AEs reported belonged to the safety topic ‘upper and not otherwise specified respiratory tract infection’. The difference between treatment arms was driven by the PT ‘rhinitis’ reported in 3 (11.5%) patients in the nintedanib group and in 0 patients in the placebo group.

Trials 1199-0337 and 1199-0378 (pooled)

At the snapshot date for the pooled analysis of trials 1199-0337 and 1199-0378, within infection safety topics, 22 (45.8%) patients were reported with AEs of upper and not otherwise specified respiratory tract infection and 3 (6.3%) patients with AEs of lower respiratory tract infection. On the PT level, the most frequently reported AEs in infections safety topics were upper respiratory tract infection (reported in 7 [14.6%] patients overall), rhinitis (reported in 6 [12.5%] patients overall), and respiratory tract infection (reported in 5 [10.4%] patients overall. None of the infection AEs were assessed by BI as indicative of a causal relationship to nintedanib.

One of the events in the safety topic ‘upper and not otherwise specified respiratory tract infection’ was classified as serious. This concerned the respiratory tract infection of one patient in trial 1199-0378. The patient had to be hospitalised and intubated. The infection was treated with cephalosporin and aminoglycoside. After aggravation of the respiratory failure, the patient was readmitted to the hospital and was discharged home on non-invasive ventilation approximately 3 weeks later.

The updated safety results provided with the interim analysis of the 1199-0378 trial.

Additional cases of cases within infection safety topic were reported in the interim analysis of the 1199-0378 trial including one case of lower respiratory tract infection.

2.6.7.3. Serious adverse events, deaths, and other significant events

Deaths

Any deaths over the whole trial were to be analysed as time-to-event endpoints for efficacy Up to DBL1 and up to DBL2, no deaths occurred over the whole trial.

The AC was to review all fatal cases and to adjudicate all deaths to either cardiac, respiratory, or other causes. No events requiring adjudication were identified in this trial up to DBL1 and up to DBL2.

Trials 1199-0337 and 1199-0378 (pooled)

At the snapshot date for the pooled analysis, no deaths occurred during the nintedanib exposure in trials 1199-0337 and 1199-0378.

After the snapshot date for the pooled analysis 1 case of death was reported. This patient died 8 months after discontinuation of the trial drug (approximately 7 months after end of the REP; reason for discontinuation: burden of study procedures).

Serious adverse events

Double-blind period

Up to DBL1, 2 (7.7%) patients receiving nintedanib and no patients receiving placebo had AEs which were considered serious. This comprised 1 patient reported with an SAE of respiratory distress and an SAE of increased carbon dioxide and 1 patient reported with a SAE of COVID-19. All SAEs reported up to DBL1 were also considered severe.

Compared with data based on DBL1, 1 more patient was reported with an SAE during the double-blind period up to DBL2. This comprised a 15-year-old female patient receiving placebo reported with frontal lobe epilepsy.

Trials 1199-0337 and 1199-0378 (pooled)

Over the nintedanib exposure period of both studies, 15 (27.8%) patients were reported with SAEs. At the SOC level, the most frequently reported SAEs were ‘respiratory and thoracic disorders’ (8 patients, 14.8%), which were presumably related to the underlying ILD diagnoses. At the PT level, the only SAEs reported in more than one patient were interstitial lung disease (3 patients, 5.6%) and COVID-19 (2 patients, 3.7%).

Table 62: Serious adverse events – TS

System organ class PT	Total N (%)	 Rate/100 pt-yrs
Number of patients	54 (100.0)	
Patients with any SAE	15 (27.8)	26.61
Respiratory, thoracic and mediastinal disorders	8 (14.8)	12.03
Interstitial lung disease	3 (5.6)	4.47
Dyspnoea	1 (1.9)	1.44
Pneumothorax	1 (1.9)	1.44
Pulmonary hypertension	1 (1.9)	1.44
Respiratory distress	1 (1.9)	1.44
Respiratory failure	1 (1.9)	1.43
Infections and infestations	3 (5.6)	4.52
COVID-19	2 (3.7)	3.01
Respiratory tract infection	1 (1.9)	1.43
Hepatobiliary disorders	3 (5.6)	4.55
Drug-induced liver injury	1 (1.9)	1.46
Hepatitis	1 (1.9)	1.45
Liver injury	1 (1.9)	1.47
Gastrointestinal disorders	2 (3.7)	2.98
Abdominal pain	1 (1.9)	1.45
Tooth development disorder	1 (1.9)	1.47
Blood and lymphatic system disorders	1 (1.9)	1.44
Sickle cell anaemia with crisis	1 (1.9)	1.44
Congenital, familial and genetic disorders	1 (1.9)	1.43
Sickle cell anaemia	1 (1.9)	1.43
Eye disorders	1 (1.9)	1.44
Optic atrophy	1 (1.9)	1.44
Immune system disorders	1 (1.9)	1.43
Transplant rejection	1 (1.9)	1.43
Investigations	1 (1.9)	1.44
Carbon dioxide increased	1 (1.9)	1.44
Psychiatric disorders	1 (1.9)	1.44
Suicidal ideation	1 (1.9)	1.44
Vascular disorders	1 (1.9)	1.46
Neurogenic shock	1 (1.9)	1.46

pt-yrs: patient-years

2.6.7.4. Laboratory findings

Table 63: Patients with on-treatment elevations in liver enzymes and bilirubin over the whole trial (up to DBL2) – TS

		Placebo/nintedanib		Nintedanib/nintedanib	
		N	%	N	%
Number of patients		13	100.0	26	100.0
Maximum ALT	≥3x ULN	0	0	2	7.7
	≥5x ULN	0	0	1	3.8
	≥8x ULN	0	0	0	0
Maximum AST	≥3x ULN	0	0	0	0
	≥5x ULN	0	0	0	0
	≥8x ULN	0	0	0	0
Maximum ALT and/or AST	≥3x ULN	0	0	2	7.7
	≥5x ULN	0	0	1	3.8
	≥8x ULN	0	0	0	0
Maximum total bilirubin	≥1.5x ULN	0	0	1	3.8
	≥2x ULN	0	0	0	0
Maximum ALKP	≥1.5x ULN	3	23.1	1	3.8
	≥2x ULN	2	15.4	0	0
Maximum GGT	≥3x ULN	0	0	1	3.8

ALKP: alkaline phosphatase; ALT: alanine transferase; AST: aspartate transferase; GGT: gamma-glutamyl transferase; ULN: upper level of normal

Subgroup analyses of maximum liver enzyme and bilirubin elevations.

All elevations of liver enzymes and bilirubin were reported in the subgroup of patients aged 12 to <18 years apart from 1 (12.5%) patient in the nintedanib/nintedanib group belonging to the age group of 6 to <12 years who was reported with an ALT elevation of ≥5x ULN based on data up to DBL2. One elevation of alkaline phosphatase ≥1.5x ULN and ≥2x ULN in the placebo/nintedanib group was reported in a subgroup of male patients; the remaining elevations were reported in females.

Trials 1199-0337 and 1199-0378 (pooled)

Elevations in liver enzymes and bilirubin, based on central laboratory assessments, are summarised in the table below.

Over the nintedanib exposure period of both trials, 3 (5.6%) patients with normal ALT values at baseline had possibly clinically significant abnormalities with regard to ALT, and 1 (1.9%) patient with normal gamma-glutamyl transferase (GGT) values at baseline had a possibly clinically significant abnormality with regard to GGT.

Haematology parameters and differentials

Double-blind period

The majority of patients in both treatment groups had values of haematology parameters within the normal ranges at baseline and the values remained within these ranges during the double-blind period up to DBL1 and up to DBL2,

The majority of patients in both treatment groups had values of differentials within the normal ranges at baseline and during the double-blind period up to DBL1, apart from monocytes/leukocytes for which 5 (19.2%) patients in the nintedanib group and 2 (15.4%) patients in the placebo group had the values below the normal range and 10 (38.5%) patients in the nintedanib group and 6 (46.2%)

patients in the placebo group had the values above the normal range during the double-blind period up to DBL1. Based on data up to DBL2, for monocytes/leukocytes, 1 additional patient in the nintedanib group had at least 1 on-treatment value below the normal range

Possibly clinically significant abnormality in eosinophils/leukocytes (i.e. eosinophil to leukocyte ratio of >10%) was reported for no patients in the nintedanib group and in 1 out of 12 patients (8.3%) in the placebo group.

Table 64: Frequency of patients with possibly clinically significant abnormal values in haematology parameters and differentials during the double-blind period (up to DBL1) – TS

Low High

	Low		High	
	Placebo n/N (%)	Nintedanib n/N (%)	Placebo n/N (%)	Nintedanib n/N (%)
Haematology				
Erythrocytes	0/13 (0)	1/26 (3.8)	0/13 (0)	0/26 (0)
Leukocytes	0/13 (0)	1/26 (3.8)	0/13 (0)	0/26 (0)
Differentials				
Eosinophils/leukocytes	0/12 (0)	0/26 (0)	1/12 (8.3)	0/26 (0)

Compared with data up to DBL1, 1 more patient receiving placebo was reported with possibly clinically significant elevations in haematocrit and leukocytes. No additional possibly clinically significant abnormalities in eosinophils/leukocytes (i.e. eosinophil to leukocyte ratio of >10%) were reported based on data up to DBL2.

Trials 1199-0337 and 1199-0378 (pooled)

Table 65: Frequency of patients with possibly clinically significant abnormal values in haematology parameters and differentials – TS

Number of patients	Patients in Lab, N	Low n (%)	High n (%)
Haematology			
Ery. Mean Corpuscular Volume	54	0	0
Erythrocytes	54	1 (1.9)	0
Haematocrit	51	2 (3.9)	2 (3.9)
Haemoglobin	52	1 (1.9)	3 (5.8)
Leukocytes	53	4 (7.5)	1 (1.9)
Platelets	54	0	0
Differentials			
Eosinophils	48	0	1 (2.1)
Eosinophils/Leukocytes	53	0	1 (1.9)
Neutrophils	2	0	0
Segmented neutrophils	48	2 (4.2)	0
Segmented neutrophils/Leukocytes	48	1 (2.1)	0

Coagulation parameters

Double-blind period

Only 1 case of possibly clinically significant abnormalities in coagulation parameters was reported during the double-blind period up to DBL1. One (3.8%) patient receiving nintedanib was reported with

a high value of INR. No new possibly clinically significant abnormalities in coagulation parameters were reported during the double-blind period up to DBL2

Trials 1199-0337 and 1199-0378 (pooled)

Over the exposure period of both trials, 3 (5.6%) patients were reported with possibly clinically significant abnormalities in prothrombin international normalised ratio (INR) and 1 (1.9%) patient in prothrombin time.

Electrolytes, clinical chemistry, and urinalysis parameters

Double-blind period, whole trial, and nintedanib-exposure period

For electrolytes, clinical chemistry, and urinalysis parameters, the majority of patients in both treatment groups had values within the normal ranges at baseline and remained within these ranges during the double-blind period the whole trial and the nintedanib-exposure period up to DBL1.Within electrolytes, shifts from normal to high values reported for >10% of patients in any treatment group over the double-blind period were observed for calcium and phosphate. For a total of 6 (23.1%) patients on nintedanib and 2 (15.4%) patients on placebo, values of calcium shifted from normal to high over the double-blind period, and for 1 (3.8%) patient on nintedanib and 3 (23.1%) patients on placebo, values of phosphate shifted from normal to high for 1 additional patient, values of calcium shifted from normal to high over the whole trial compared with the double-blind period. No further changes in the frequency of patients with values of phosphate shifting from normal to high were observed over the whole-trial period up to DBL1.

Based on data up to DBL2, for electrolytes, clinical chemistry, and urinalysis parameters, the majority of patients in both treatment groups had values within the normal ranges at baseline and remained within these ranges during the double-blind period and the whole trial.

Like for data up to DBL1, within electrolytes, shifts from normal to high values reported for >10% of patients in any treatment group over the double-blind period up to DBL2 were observed for calcium and

Phosphate. Compared with data based on DBL1, up to DBL2, no additional patients were reported with values of calcium or phosphate that shifted from normal to high during the double-blind period and over the whole trial.

During the double-blind period up to DBL1, possibly clinically significant abnormalities were reported for phosphate (high in 2 out of 23 [8.7%] patients on nintedanib and in 2 out of 9 [22.2%] patients on placebo) and potassium (high in 1 [3.8%] patient on nintedanib and in no patients on placebo. No additional possibly clinically significant abnormalities were reported during the double-blind period up to DBL2 as well as over the whole trial up to DBL1 and up to DBL2.

Trials 1199-0337 and 1199-0378 (pooled)

A total of 4 patients were reported with possibly clinically significant abnormalities in electrolytes, clinical chemistry, and urinalysis parameters during the nintedanib-exposure period of trials 1199-0337 and 1199-0378 pooled. Possibly clinically significant abnormalities were reported for phosphate (high in 3 [7.9%] patients) and potassium.

Vital signs

Whole trial

Based on data up to DBL1 and up to DBL2, there were no notable changes in the mean blood pressure and pulse rate values over the whole trial. No AEs relevant to the medical concept of hypertension were reported.

Body weight and body mass index

The mean (SD) change from baseline in body weight at Week 24 of treatment up to DBL1 was -0.2 (1.9) kg in the nintedanib group and 1.8 (4.1) kg in the placebo group. Based on data up to DBL1, the mean (SD) minimum relative change from baseline in body weight (i.e. maximum loss of body weight) over the whole trial was -2.95 (4.13)% in the nintedanib/nintedanib group and -0.64 (3.50)% in the placebo/nintedanib group.

In line with data up to DBL1, based on data up to DBL2, the mean (SD) change from baseline in body weight at Week 24 of treatment was -0.3 (2.1) kg in the nintedanib group and 1.4 (3.8) kg in the placebo group. The mean (SD) minimum relative change from baseline in body weight (i.e. maximum loss of body weight) over the whole trial up to DBL2 was -3.23 (4.30)% in the nintedanib/nintedanib group and -1.27 (3.85)% in the placebo/nintedanib group. Compared with data up to DBL1, 1 additional patient lost more than 10% of their body weight at some point over the whole trial up to DBL2.

Trials 1199-0337 and 1199-0378 (pooled)

The mean (SD) minimum relative change from baseline in weight was -2.61 (10.35)% over the nintedanib exposure period of both trials. A relative decrease of >0% to 5% was observed in 27 (50.0%) patients, a relative decrease of >5% to 10% in 10 (18.5%) patients, and a relative decrease of >10% in 5 (9.3%) patients. For the remaining patients (12 patients, 22%) a relative increase was observed.

At some point over the nintedanib-exposure period, 5 (10.4%) patients (lost more than 10% of their body weight compared with their baseline value. The weight loss was reported as an AE of decreased weight for 3 of these patients . All the AEs were mild or moderate in intensity, non-serious, and assessed as not drug related by the investigator.

- Patient with a baseline weight of 32.0 kg and a baseline condition of oesophageal dysmotility associated with systemic sclerosis, who had been reported with a weight loss of >10% in trial 1199-0337 (see the subsection above), further lost body weigh up to a maximum of 7.0 kg decrease at their last available assessment before the snapshot date in trial 1199-0378, on Day 754 of nintedanib treatment.
- Patient had caeliac disease and oesophageal sclerosis associated with systemic sclerosis as baseline conditions. The weight of this patient decreased from 40.8 kg at baseline to a minimum of 33.5 kg on Day 221
- Patient had a baseline weight of 32.5 kg which decreased to 28.8 kg on Day 259. This patient had a severe underlying respiratory disease which progressed significantly over both trials
- Patient had a baseline weight of 42.3 kg. The weight of this patient decreased to 37.0 kg at nintedanib discontinuation and further to 36.4 kg at the EoT visit. The patient had anorexia nervosa and sickle cell disease reported as baseline conditions.The clinical course of this patient was complicated by a new episode of anorexia nervosa, 2 episodes of sickle cell anaemia with crisis, and ILD progression.
- Patient randomised to nintedanib with a body weight of 47 kg at baseline was reported with a maximum of 6 kg decrease in weight at an EoT visit at Week 24 and at a follow-up visit at

Week 36. The weight loss was not reported as an AE by the investigator, but the patient was reported with an AE of decreased appetite (reported term: anorexia) which, according to the investigator's assessment, was not related to trial medication. The patient had gastrooesophageal reflux disease reported as a baseline condition.

All 5 patients with a decrease in body weight of >10% had risk factors for weight decrease, such as progression of underlying respiratory disease or other comorbidities (such as anorexia nervosa, oesophageal dysmotility, respiratory tract infection). Two of the 5 patients gained weight while treatment with nintedanib was continued.

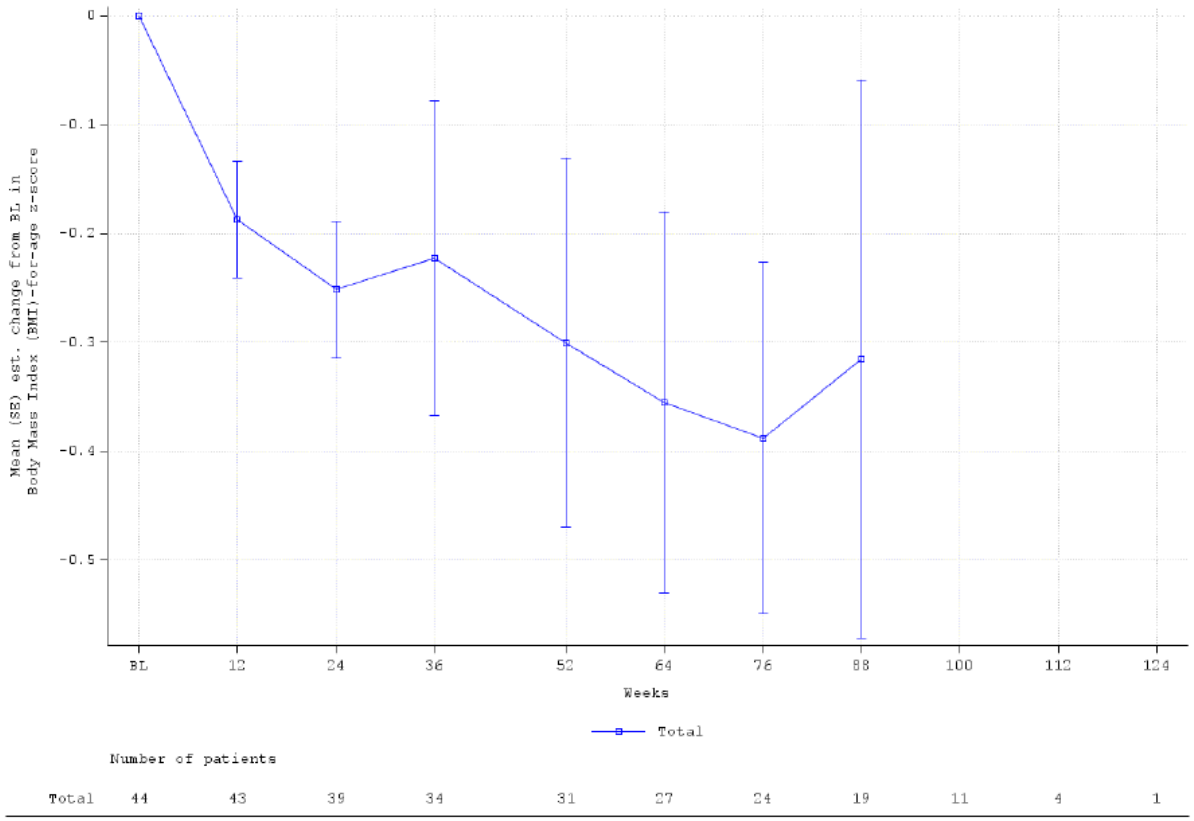
Change in BMI-for-age z-score from baseline to Week 24 and Week 52 (further safety endpoint)

In order to account for variation in BMI due to the age and gender of the paediatric patients, the change from baseline in BMI was also calculated as BMI-for-age z-scores (BAZ), using the respective WHO Reference centile curves. Up to DBL1 and up to DBL2, due to differing length of the observation period for individual patients, only limited data were available for Week 52.

Based on data up to DBL2, the adjusted mean changes from baseline in BAZ at Weeks 24 (nintedanib: -0.30 [95% CI -0.48, -0.13], placebo: 0.08 [95% CI -0.16, 0.32]) and 52 (nintedanib: -0.29 [95% CI -0.61, 0.03], placebo: -0.02 [95% CI -0.45, 0.42]) were similar to those observed based on data up to DBL1.

Trials 1199-0337 and 1199-0378 (pooled)

The mean (SD) BAZ was -0.52 (1.75) at baseline. The adjusted mean (SE) of the absolute change from baseline was -0.34 (0.17) at Week 52 (n=33) and -0.33 (0.23) at Week 88 (n=22).



Height, sitting height, and leg length

Change from baseline in height, sitting height, leg length at Weeks 24, 52, 76, and 100 (secondary safety endpoint)

Up to DBL1, due to differing length of the observation period for individual patients, only limited data are available for height, sitting height, and leg length for Week 52 and 76, and no

data are available for Week 100 Therefore, based on data up to DBL1, adjusted mean of absolute changes from baseline in height, sitting height, and leg length could be calculated up to Week 24 only. Based on data up to DBL2 adjusted mean of absolute changes from baseline in height and leg length were additionally calculated for up to Week 36, up to Week 52, and up to Week 76 timepoints.

Height (standing)

Based on data up to DBL1, adjusted mean changes from baseline in height at Week 24 were 1.2 cm (95% CI 0.7, 1.7) in the nintedanib group and 1.5 cm (95% CI 0.7, 2.2) in the placebo group showing normal linear growth and suggesting no relevant effect of nintedanib on growth. Similar results were obtained in the sensitivity analysis excluding patients with closed epiphyses.

Based on data up to DBL2, adjusted mean changes from baseline in height at Weeks 12 to 76 showed normal linear growth, further indicating that there is no relevant effect of nintedanib on growth, as previously suggested by data up to DBL1. Similar results were obtained in the sensitivity analysis excluding patients with closed epiphyses based on data up to DBL2.

Trials 1199-0337 and 1199-0378 (pooled)

Height (standing)

The mean (SD) height at baseline was 148.2 (17.4) cm. The adjusted mean (SE) absolute change from baseline was 2.4 (0.3) cm at Week 52 (n=33) and 4.7 (0.6) cm at Week 100 (n=20).

Change in height-for-age z-score from baseline to Week 24 and Week 52 (further safety endpoint)

Based on data up to DBL2, adjusted mean changes from baseline in HAZ at Week 24 were -0.05 (95% CI -0.11, 0.01) in the nintedanib group and -0.03 (95% CI -0.12, 0.05) in the placebo group. At Week 52, the adjusted mean changes from baseline were -0.05 (95% CI -0.18, 0.07) in the nintedanib/nintedanib group and -0.02 (95% CI -0.19, 0.15) in the placebo/nintedanib group. Changes are considered not clinically relevant and support the observation of normal linear growth in both treatment groups.

Trials 1199-0337 and 1199-0378 (pooled)

The mean (SD) HAZ was -0.81 (1.42) at baseline. The adjusted mean (SE) of the absolute change from baseline was -0.06 (0.04) at Week 52 (n=33) and -0.07 (0.07) at Week 100 (n=17), suggesting normal linear growth in patients receiving nintedanib treatment.

Treatment-emergent pathological findings of the epiphyseal growth plate on imaging

Trials 1199-0337 and 1199-0378 (pooled)

In trials, MRI or x-ray assessments of growth plates were conducted in all patients with open physes.

Overall, 5 (9.3%) patients were reported with at least one treatment-emergent pathological finding:

Patient was reported with ‘other findings, potentially pathological’ at Week 24 of the double-blind nintedanib treatment in trial 1199-0337. The reported findings were low T1 and T2 signal lesions in distal femur and proximal tibia, which largely resolved at Week 36 and completely resolved at Week 52. The corresponding AE reported in trial 1199-0337 is ‘bone lesion’ on the PT level. In a follow-up examination at Week 76, the patient was reported with ‘other findings’ potentially pathological’ at the proximal tibia, which, as per the central reader assessment, appeared similar to the findings reported in this patient in the previous time points. The corresponding AE reported in trial 1199-0378 is ‘bone disorder’ on the PT level. All pathological findings resolved at Week 100, while treatment with nintedanib was ongoing. As per the SMC review, the findings are unrelated to treatment with nintedanib, and the tibial metaphysis is likely physiologic.

Patient was reported with potentially pathological metaphyseal lines at distal femur after 12 weeks of nintedanib treatment in trial 1199-0337. This patient had potentially pathological metaphyseal lines at the proximal tibia at baseline examination. The investigator assessed the findings as not pathological and no corresponding AE was reported by the investigator. No other pathological findings in the bone were reported for this patient up to Week 100.

Patient , a 14-year-old female, was reported with potentially pathological progressive narrowing of lucent growth plate margin of proximal tibia/distal femur compared with the baseline timepoint. No pathological findings in the bone were reported for this patient in subsequent examinations up to Week 76 and no corresponding AE was reported. The SMC concluded that the findings were physiologic as no further growth was expected in this patient and recommended trial drug continuation.

A 13-year-old female patient was reported with potentially pathological progressive narrowing of lucent growth plate margin of proximal tibia/distal femur at the EoT visit of trial 1199-0337. As per the SMC review, the changes were most likely physiologic given the patient’s age. At Week 76, the patient was additionally reported with other potentially pathological findings at the distal femur (‘NOF distal femur, unchanged’) and at the proximal tibia (small sclerotic focus, unchanged). The additional findings resolved spontaneously (not present on the bone imaging at Week 100), while treatment with nintedanib was maintained. As per the SMC review, the additional findings reported are physiological and unlikely to be related to nintedanib.

A 10-year-old female patient was reported with potentially pathological progressive narrowing of lucent growth plate margin at distal femur and proximal tibia at Week 52 of nintedanib treatment. The finding was completely resolved at Week 76. As per the central reviewer’s comment, the apparent narrowing of the physis noted previously was probably due to differences in projection, as on imaging results at Week 76 the physis did not appear narrowed compared with the initial baseline assessment. As per the investigator’s assessment, none of the 2 potentially pathological findings were reported as AEs.

Table 66: Frequency of patients with treatment-emergent pathological findings on the epiphyseal growth plate on imaging during the pooled nintedanib-exposure period of trials 1199-0337 and 1199-0378 – TS

	Total	
	N	%
Number of patients	54	100.0
Number of patients with at least 1 pathological finding[1]	5	9.3
Pathological findings at the distal femur	5	9.3
Thickening of the epiphyseal growth plates	0	0.0
Swelling of articular cartilage	0	0.0
Metaphyseal lines, if judged pathological	1	1.9
Narrowing of the lucent growth plate margin, if judged pathological	3	5.6
Other findings, if judged pathological[2]	2	3.7
Pathological findings at the proximal tibia	4	7.4
Thickening of the epiphyseal growth plates	0	0.0
Swelling of articular cartilage	0	0.0
Metaphyseal lines, if judged pathological	0	0.0
Narrowing of the lucent growth plate margin, if judged pathological	3	5.6
Other findings, if judged pathological	2	3.7

Treatment-emergent pathological findings on dental examination or imaging

Trials 1199-0337 and 1199-0378 (pooled)

In trials 1199-0337 and 1199-0378, dental imaging and examination were conducted regularly in all patients.

Overall, 26 (48.1%) patients had at least 1 on-treatment pathological finding on dental examination or

Imaging. With regard to dental imaging, the most frequent findings were impacted permanent teeth (8 patients, 14.8%) and stunted growth of the dental root (6 patients, 11.1%).

On dental imaging, stunted growth of the dental root was reported in 6 (12.5%) patients All these cases were reported during the double-blind period of trial 1199-0337. No additional patients were reported with stunted growth of the dental root up to snapshot date (a maximum of 148 weeks of nintedanib-exposure period in trials 1199-0337 and 1199-0378). Other pathological findings on dental imaging reported up to Week 148 of nintedanib exposure in trials 1199-0337 and 1199-0378 included impacted permanent teeth in 8 (16.7%) patients, additional findings (such as cysts, abscesses, solid lesions, bone abnormalities) in 6 (12.5%) patients, other findings in 4 (8.3% patients, and extra/supernumerary teeth in 1 (2.1%) patient.

Table 67: Frequency of patients with treatment-emergent pathological findings on dental examination or imaging during the pooled nintedanib-exposure period of trials 1199-0337 and 1199-0378 – TS

	Total	
	N	%
Number of patients	54	100.0
Patients with pathological findings on dental examination or imaging	26	48.1
Dental examination		
Patients with pathological findings[1]	19	35.2
Dental imaging		
Patients with stunted growth of dental root[2]	6	11.1
Patients with accelerated growth of dental root[3]	0	0.0
Patients with extra/supernumerary teeth	1	1.9
Patients with impacted permanent teeth	8	14.8
Patients with additional findings[4]	6	11.1
Other findings	4	7.4

2.6.7.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.7.6. Safety in special populations

Apart from the paediatric study discussed here, no additional studies in special populations were performed.

2.6.7.7. Immunological events

4 (7.4%) patients were reported with rash (PTs rash, rash maculo-papular, and rash pruritic), and 1 (1.9%) patient was reported with pruritus.

2.6.7.8. Safety related to drug-drug interactions and other interactions

Interaction studies have only been performed in adults.

2.6.7.9. Discontinuation due to adverse events

In the context of this section, treatment discontinuation was defined as being premature (i.e. treatment terminated before the planned treatment end) and permanent (i.e. no restart of trial treatment at a later time in the trial).

Double-blind period

Up to DBL1, 1 (3.8%) patient in the nintedanib group discontinued trial medication prematurely because local bone imaging interpretation suggested a potential premature fusion of the epiphyses. This AE was reported at Week 10 based on the investigator's judgment of 'slight narrowing of epiphyseal (growth) plates'. This finding, however, was not confirmed by the central review and the SMC assessment. The status of epiphyseal closure was open at Week 12 and in the follow-up at Weeks 24 to 52.

Compared with the data up to DBL1, 1 more AE leading to premature discontinuation of trial medication was reported during the double-blind period based on data up to DBL2
It comprised 1 patient with liver injury in the nintedanib group. The AE was non-serious, mild in intensity, and drug related.

No AEs leading to discontinuation of trial medication were reported in the placebo group up to DBL1 and up to DBL2.

Trials 1199-0337 and 1199-0378 (pooled)

Over the nintedanib exposure period of both trials, 3 (5.6%) patients (incidence rate: 4.32/100 patient-years) were reported with an AE leading to discontinuation of nintedanib. The respective PTs were epiphyses premature fusion, liver injury, and weight decreased.

2.6.7.10. Post marketing experience

Nintedanib is not yet registered for commercial use in paediatric patients in any part of the world. Nintedanib (Ofev), 100 mg and 150 mg soft capsules, has been approved as treatment for adult patients with idiopathic pulmonary fibrosis (IPF), systemic sclerosis (SSc)-associated ILD, and chronic fibrosing ILD with a progressive phenotypge. It was first approved in the USA on 15 Oct 2014 and in the EU/EEA on 15 Jan 2015. Information on the post marketing experience in adults is provided in the most recent PBRER of Ofev.

Until the PSUR data lock point of 15 Apr 2023, off-label use of Ofev in paediatric patients was documented for 11 patients. Eight of these 11 patients reported no AEs. Two patients reported non-serious gastrointestinal events. The remaining case concerned a 9 year-old male patient, who died 112 days after the start of treatment with Ofev. There is no other information available for this case, preventing a significant causality assessment. Overall, no safety issue has been identified based on the cases of off-label use in the paediatric population.

2.6.8. Discussion on clinical safety

Exposure to nintedanib

The safety data on the use in children come from two clinical trials, 1199-0337 and 1199-0378. 39 paediatric patients were enrolled to the 1199-0337 trial (13 to the placebo group and 26 to the nintedanib group). 49 children were enrolled to the extension study (1199-0378) including 33 children who rolled over from trial 1199-0337 and 16 new patients who directly entered trial 1199-0378. In patients who received nintedanib, the median (range) duration of exposure was 78.14 (2.8 to 150.7) weeks; the mean (SD) exposure was 70.06 (46.67) weeks. Half of the patients were treated with nintedanib for more than 76 weeks, with 6 (11.1%) patients on nintedanib for more than 124 weeks.

Thera are concerns in relation to the small number of paediatric patients, especially children under 12 years of age enrolled to studies (17 children under 12 were enrolled to both studies). Younger patients could be at higher risk of development of adverse reactions due to their immaturity as there is a risk that nintedanib could affect growth and teeth development. This is particularly relevant in respect to the long-term safety data which are limited. Although, the extension study is ongoing, the number of newly recruited younger children is still small. The applicant was asked whether additional safety data could be generated post-marketing, for example through the use of registries.

Adverse events

Comparative safety data are available for 24 weeks. In the double-blind period of the 1199-0337 trial, AEs were reported by most patients (84.6%) in both treatment groups. SAEs were reported at low

frequency, in 7.7% of patients in each treatment group. The proportion of patients with AEs considered drug-related was slightly higher in the nintedanib group than in the placebo group (53.8% versus 38.5%, respectively). During the 24 weeks double-blind period the AEs leading to discontinuation of trial medication and severe AEs were reported at low frequency (in 2 patients each) and only in the nintedanib group.

At the snapshot date for the pooled interim analysis, at least 1 treatment-emergent AE during the nintedanib-exposure period of trials 1199-0337 and 1199-0378 was reported 100 % of children. SAEs were reported in 15 (27.8 %) children including 8 in the extension study, drug-related AEs were reported in 39 (72.2%) children (27 in the extension study) and AEs leading to discontinuation in 3 children (1 new event reported in the extension study).

Common AEs

The most frequently reported AEs during the double-blind period of 1199-0337 trial belonged to the SOC ‘gastrointestinal disorders’. The second most common SOC was the SOC ‘Infections and infestations’ followed by the SOC ‘General disorders and administration site conditions’ and ‘Respiratory, thoracic and mediastinal disorders.

In relation to PTs reported in paediatric patients, many of these were in line with those seen in adults; however, due to the small sample size the number of these events was small.

Within the SOC ‘gastrointestinal disorders’, diarrhoea was the most frequently reported PT in the nintedanib group. It was reported by 10 (38.5%) patients treated with nintedanib and 2 (15.4%) patients receiving placebo. Vomiting was also more frequently reported in the treatment arm, while there was no increase in the frequency of abdominal pain and nausea. Diarrhoea, nausea, abdominal pain and vomiting are known adverse drug reactions associated with nintedanib treatment and they are listed in the SmPC with the frequency very common. Decreased appetite and dehydration were also reported in the nintedanib group.

Similar pattern of AEs was seen during the nintedanib-exposure period of trials 1199-0337 and 1199-0378. Diarrhoea was the most frequently reported (by 51.9% of children), followed by vomiting, abdominal pain and nausea. The exposure adjusted analysis as provided by the MAH does not indicate an increase in frequencies of these AEs associated with longer exposed with exception of AE decreased weight. AEs of weight decreased was reported by 2 (5.4%) children in 1199-0337 trial and 5 (10.4%) children in the extension trial (see further discussion below).

Severe AEs

In total, severe AEs were reported in 6 children in trial 1199-0337, including single cases of COVID−19 infection, respiratory distress, tooth development disorder (2 cases), carbon dioxide increased and ligament sprain. Further, 8 children experienced severe AEs in the extension study, including 7 new severe AEs within the SOC Respiratory, thoracic, and mediastinal disorders (Interstitial lung disease, dyspnea, epistaxis, pneumothorax pulmonary hypertension and Respiratory failure). These AEs were likely to be related to the disease progression. Other cases included severe AE of abdominal pain and vomiting, severe case of wight decrease, respiratory tract infection, hepatitis (discussed below) and case of sickle cell anaemia (reported in a patient with a history of this disease).

Drug-related AEs

In the double-blind period up to DBL2, the proportion of patients with AEs which were considered drug-related by the investigator was higher in the nintedanib group (14 patients; 53.3%) than in the placebo group (5 patients; 38.5%).

The most frequent PTs which were considered related to the treatment are known to be associated with nintedanib such as diarrhoea, nausea, vomiting and abdominal pain. However, some additional PTs (not listed in the SmPC) were also considered related to the treatment by investigators, including epiphyses premature fusion, tooth development disorder, dental cyst, lower gastrointestinal haemorrhage, insomnia, menstruation delayed, hot flush, anxiety, arthralgia, chest discomfort, cough, exertional dyspnoea and madarosis. During the original submission the MAH provided discussion on these AEs and it can be agreed that based on the data presented so far no association can be found with nintedanib treatment.

5 cases of treatment-related weight decrease were reported in the extension study. Weight decrease is a known ADR associated with nintedanib treatment.

Additional PTs considered related to the treatment, were reported in the extension study including flatulence, gastritis, gastrooesophageal reflux disease, neutrophil count decreased, pyrexia, bone disorder, failure to thrive, cholelithiasis, tooth hypoplasia and suicidal ideation. These AEs were reported by only 1 patient each at the PT level, thus not listed in the SmPC.

Serious adverse events and deaths, other significant events

In total SAEs were reported in 16 children, including in 3 children in during double-blind period and 5 children during the open-label period of 1199-0337 study. Further 8 children experienced SAEs in the extension study.

All SAEs expect frontal lobe epilepsy were reported in patients treated with nintedanib. Some SAEs such as dyspnea, pneumothorax, respiratory failure and distress, and pulmonary hypertension are likely related to the underlying disease. Other SAEs such as abdominal pain, tooth development disorder, drug-induced liver injury and liver injury were considered related to the study treatment. On Day 270 of nintedanib treatment, the patient was reported with investigator-defined drug related.

One child developed SAE of suicidal ideation of moderate intensity. On the same day, the patient was reported with non-serious and not drug-related bipolar disorder of moderate intensity. The SAE of suicidal ideation resolved while on unchanged dose of nintedanib.

At PT level only interstitial lung disease and Covid-19 were reported by more than 1 patient. For further discussion on SAEs within the SOC Hepatobiliary disorders (Drug-induced liver injury, Liver injury and Hepatitis) please see below.

No deaths occurred during the nintedanib exposure in trials 1199-0337 and 1199-0378, however one patient died 8 months after discontinuation of the trial drug.

Tooth disorders

Tooth development disorders were observed in preclinical studies. In this respect the SmPC states: "*In repeat dose toxicology studies in young rats, irreversible changes of enamel and dentin were observed in the continuously fast-growing incisors, but not in premolars or molars*". It is noted that adverse effect on teeth have been reported for other VEGF TKIs also.

In the 1199-0337 trial dental imaging was conducted in patients at baseline and at 24 weeks, 52 weeks and every 48 weeks thereafter until the end of the study. Dental examination was performed more frequently. Dental examination and imaging was continued to be investigated in 1199-0378 trial.

Results of dental examination and dental imaging

In general, at week 24 pathological findings on dental examination as well as on imaging were reported more frequently in patients treated with nintedanib as compared to those on placebo. Based

on data up to DBL2, 5 (19.2%) patients in the nintedanib group and 1 (7.7%) patient in the placebo group reported pathological findings on dental examination.

In relation to the dental imaging results, stunted growth of the dental root was reported in 6 (23.1%) patients in the nintedanib group and no patients in the placebo group up to Week 24. Additional findings were also more frequently reported in patients on nintedanib than on placebo.

Dental disorders reported as AEs

Dental caries

Based on pre-clinical findings, dentopathy is considered as a class effect of all vascular endothelial growth factor receptor (VEGFR) inhibitors. However, as indicated by applicant, although seen for other VEGFR inhibitors, dental caries and alteration of dentin composition were not observed in pre-clinical studies conducted with nintedanib. 15 children reported an AE of dental caries while on treatment with nintedanib in 1199-0337 and 1199-0378 trials; however, most of these children reported dental caries also at baseline. All cases of dental caries were not considered related to the study treatment by investigators.

Based on limited data available it can be agreed that there is no clear association between the development of dental caries and nintedanib treatment. However, this safety concern should be continued to be monitored as the risk cannot be fully excluded taking into consideration the limited safety data available for children under the age of 12 who were exposed to treatment with nintedanib.

Tooth development disorders

In the study there was an imbalance in tooth development disorders as assessed by central review of the panoramic dental imaging. Stunted growth of the dental root was reported in 6 (23.1%) patients in the nintedanib group and no patients in the placebo group up to Week 24. Four cases of tooth development disorder were considered related to the study drug; 2 cases were considered as severe.

In relation to stunted growth of the dental root the MAH clarified that for 5 out of 6 patients, no indication of stunted growth of dental root was reported by the central review at Week 52 and in the follow-up imaging up to Week 100 of nintedanib treatment the 1199-0378 extension study.

However, for one patient (age 6 at enrolment) pathological findings were still described for 4 of 10 teeth at week 52: on follow-up at week 52, stunted growth was reported for the anterior teeth (. As this patient did not enrol to the extension trial 1199-0378 (for reasons not related to safety), further data on dental imaging are not available for this patient and therefore some uncertainties regarding relationship to the study treatment remain.

A single new patient was reported with an AE in the safety topic of ‘tooth development disorders’ in the trial 1199-0378 (AE of ‘tooth hypoplasia’ (verbatim ‘enamel hypoplasia’). However, this case was confounded by a medical history of Ewing’s sarcoma of lower jaw and the chemotherapy received before the eruption of the permanent teeth.

Based on the current data, there is no evidence to confirm the potential risk of ‘tooth development disorders’ in the paediatric population. However, there is still uncertainty in relation to the potential effects of nintedanib on tooth development in humans as the number of exposed children especially those younger than 12 years of age is small. Information on the uncertainties of a potential impact on tooth development and recommendations for monitoring, is included in the proposed SmPC (sections 4.2, 4.4, 4.8). In addition, ‘Effect on tooth development disorders in the paediatric population’ is an important potential risk for nintedanib. Further, any AEs of tooth development disorders will be discussed at each PSUR.

Liver safety

Liver abnormalities (i.e. liver injury, hepatitis or asymptomatic increase in liver enzymes) were reported 10 (18.5%) children treated with nintedanib in trials 1199-0337 and 1199-0378. Such abnormalities were not seen in patients on placebo.

Liver abnormalities were reported in 2 patients in double-blind period, in 4 patients during the open-label period and in 4 new patients in the extension study.None of the patients reported with a hepatic event fulfilled the Hy's law criteria of ALT and/or AST elevations ≥3x ULN concurrent with an elevation in total bilirubin ≥2x ULN.

One case of DILI was reported in 13-year-old female patient. Sixty days after the first intake of the open-label trial medication, the patient experienced a medically important serious adverse event of drug-induced liver injury of mild intensity. In this patient there was elevation in ALT >5×ULN but bilirubin was normal. The treatment was interrupted, and the event of drug-induced liver injury resolved after 54 days. Following normalisation of liver enzymes, the treatment with nintedanib was restarted in the extension trial 1199-0378 with no recurrence of hepatic abnormalities. Of note, in this patient the exposure was higher than observed for the other paediatric patients.

In a single case the hepatic event associated with abdominal pain led to treatment discontinuation.

In all other 8 cases the hepatic event was managed as per clinical trial protocols (i.e., dose reduction/treatment interruption if ALT and/or AST elevations ≥3x ULN were reported). In all these cases the hepatic event resolved and treatment with nintedanib could be continued.

The frequency and incidence rate of hepatobiliary disorders was similar between children and adults. However, the frequency and incidence rate of 'DILI' in children (based on the one case reported in children) was numerically higher than in adult patients.

The SmPC includes the following statement:

*Hepatobiliary disorders reported with nintedanib during placebo-controlled period were liver injury (3.8 %) and increased liver function test (3.8 %). Due to limited data, it is uncertain if the risk for drug-induced liver injury is similar in children as compared to adults*_(see section 4.4)."

As agreed with the MAH, the risk of DILI in the paediatric population will be closely monitored in the post-marketing setting and it will be discussed routinely in the PSURs.

Of note, DILI is listed as an important identified risk and hepatic failure is listed as an important potential risk in the RMP.

Bleeding and haematological safety

VEGFR inhibition might be associated with an increased risk of bleeding. Bleeding is listed in the SmPC as an ADR. In children receiving nintedanib bleeding events were reported including lower gastrointestinal haemorrhage [1 case], heavy menstrual bleeding [1 case], epistaxis (3 cases), haemoptysis (1 cases) and haematuria (1 case); however, these events were nonserious and in most case mild in intensity.

For some paediatric patients, asymptomatic changes in blood test results were reported including thrombocytopenia (listed as ADR in SmPC), neutropenia and leukopenia (not listed in the SmPC).

In trials 1199-0337 and 1199-03784 neutropenia/leukopenia of mild or moderate intensity was reported in 4 children and however all these cases also confounding factors. In all children the treatment with nintedanib was interrupted but after resolution it was resumed, and the recurrence of the AEs was not reported. Therefore, it can be agreed that no amendments to the SmPC is required in respect of AEs of neutropenia/leukopenia.

Infections

In total, 23 (42.6%) and 4 (7.4%) children treated with nintedanib reported upper and lower respiratory tract infection, respectively. Some imbalance in the number of infections were reported in the double-blind period in trial 1199-0337. In relation to PTs 'COVID−19' the imbalance could be partially explained by the fact that more patients in the placebo group vaccinated against COVID-19 or had COVID-19 prior to enrolment. In relation to the PT rhinitis, the difference was considered not relevant, based on the trial randomisation (i.e. 2:1 ratio for nintedanib versus placebo) and the fact that 1 of the patients had allergic rhinitis as a baseline condition. The remaining PTs were reported only once.

Based on the data in adult population, there is no evidence of an increased risk of infections with nintedanib. Based on the totality of the data as presented, it can be agreed that there is no clear association between the increased risk of infection and nintedanib treatment.

Effect on weight.

The effect on the body weight was assessed in the study, however the comparative data are available for 24 weeks only. During the double-blind period of 1199-0337 trial, looking at mean change from baseline, patients receiving nintedanib lost weight whereas patients on placebo gained weight.

In the pooled analysis of clinical trials 1199-0337 and 1199-0378, 6 patients (11.1%), were reported with an AE in the safety topic of 'weight decreased' (incidence rate 9.27 per 100 PY). All 6 patients were reported with non-serious AE of 'weight decreased'. The action taken with nintedanib in relation to 'weight decreased' was 'dose not changed' (4 patients), 'dose reduced' (1 patient), and 'drug withdrawn' (1 patient).

A significant decrease in body weight was reported in 5 children treated with nintedanib, who lost more than 10% of their body weight compared with their baseline value.

Although some patients had confounding factors , a contributing role of nintedanib to further decrease of body weight in these patients is very likely.

The applicant claims that based on the currently available data, there is no evidence to assume a different impact of nintedanib related weight decrease (a known ADR of nintedanib treatment) in children and adolescents versus adults.

The effect on weight in children is monitored in the ongoing extension study (through the assessment of Weight-for-age z-score and BMI-for-age z-score). In addition, weight decrease was added as an important identified risk in the RMP.

Musculoskeletal system disorders and growth assessment

Reversible epiphyseal growth plate alterations were observed in preclinical studies. In this respect the following statement is included in section 5.3 of the SmPC: "*thickening of epiphyseal growth plates during bone growth phases was observed and was reversible after discontinuation*". Bone and growth disorders were reported for other VEGF TKIs also.

Radiological assessments

Radiological assessments were performed in trials 1199-0337 and 1199-0378 and the results were assessed by a blinded external expert.

Up to week 52 of 1199-0337 trial, there were 5 patients treated with nintedanib with pathological findings on the epiphyseal growth plate on imaging. Although potentially pathological findings on the epiphyseal growth plate on imaging were seen for 5 patients, an AE was reported only for one patient (with bone lesion).

One child with metaphyseal lines potentially pathological at distal femur seen after 12 weeks of treatment had metaphyseal lines potentially pathological at the proximal tibia also at baseline.

In another child low T1 and T2 signal lesions in distal femur and proximal tibia were reported at week 24. The corresponding AE reported on the PT level for this patient was 'bone lesion'. As these findings were already present at baseline, it is assessed that the patient's underlying condition of osteopathy associated with long term glucocorticoid treatment could be an explanation for the event. All pathological findings resolved at Week 100, while treatment with nintedanib was ongoing.

In 3 further patients potentially pathological progressive narrowing of lucent growth plate margin was reported. However, these changes were considered (based on the central review) not pathological.

An additional AE of growth plate disorder in a patient treated with nintedanib was reported during the double-blind period. One patient in the nintedanib group was reported with an AE of premature fusion of epiphyses based on local bone imaging interpretation that suggested a potential premature fusion of the epiphyses. This AE led to trial discontinuation of trial medication. This pathological finding, however, was not confirmed by the central review as it was considered that the status of epiphyseal closure was open. Furthermore, the patient grew 1 cm from Week 0 to Week 12 while on trial medication and continued to grow in the follow-up period .).

Effect on growth

Change from baseline in height, sitting height, leg length was investigated in the study at weeks 24, 52, 76, and 100. Based on data up to DBL2, adjusted mean changes from baseline in height at Week 24 were 1.3 cm (95% CI 0.8, 1.8) in the nintedanib group and 1.3 cm (95% CI 0.6, 1.9) in the placebo group.

The adjusted mean change from baseline in HAZ at Week 24 of nintedanib treatment was -0.05 (95% CI -0.09, 0), at Week 52 of nintedanib treatment was -0.06 (95% CI -0.14, 0.02), and at Week 76 of nintedanib treatment was -0.06 (95% CI -0.15, 0.04).

The adjusted mean change from baseline in HAZ score was less than 0.5 and therefore considered not clinically relevant.

At patient level 4 patients were documented with a decrease from baseline of heigh-for-age z-score (HAZ) ≥0.5. It is noted that in these patients 0.5 threshold (indicating decrease in growth) was reached after 76 to 124 weeks from the beginning of treatment with nintedanib, which is a concern. On the other hand, it is agreed that the assessment on the effect on growth on the individual patent level is difficult due to individual variations in the growth patterns and the presence of confounding factors such as treatment with other medications (such as corticosteroids) with known effect on growth. Additional difficulties relate to the fact that there are no specific growth charts for children with chronic respiratory disease and therefore growth parameters are being compared with the expected growth in the healthy paediatric population.

The potential effect on growth will be further monitored by the MAH in post-marketing including the assessment in the ongoing extension study (with 3 years duration). Effect on bone development and growth in paediatric population is considered an important potential risk for nintedanib and this safety concern will be presented routinely in each PSUR. Adequate information including the need for monitoring has been inserted in the SmPC sections 4.2, 4.4 and 4.8.

Of note, children participating in the trial had lower mean standing height in the trial population compared with the reference population.

Effect on puberty

As indicated by the MAH, there is no plausible mechanism for a potential impact of nintedanib on puberty. As per current evidence, none of the inhibitory pathways of nintedanib (i.e. vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptors) are involved in the physiology of puberty. Further, based on data in adult patients, there is no indication of an association between nintedanib and endocrine and reproductive systems.

In both trials, the effect on puberty was evaluated based on AE collection. As of 25 Aug 2023, no paediatric patient was reported with an AE indicative of puberty disorder (no AE reported in HLTs (primary path) 'Endocrine abnormalities of puberty', 'Female gonadal function disorders' and 'Male gonadal function disorders'). As long safety data are not available, the SmPC includes a statement on the uncertainty of the potential impact on puberty, as follows: *"Long term safety data in paediatric patients are not available. There are uncertainties on the potential impact on growth, tooth development, puberty, and the risk of liver injury."*

Cardiovascular safety

No MACEs were reported in the study. However, one case of right atrial hypertrophy and one case of borderline prolonged QTc interval on ECG (439 days since the last intake of the trial medication) was reported. The MAH was requested to further discuss cardiovascular safety of nintedanib when used in children. It was clarified that right atrial hypertrophy of mild intensity reported in one child was likely to be associated with chronic pulmonary disease and early sign of right-sided structural changes associated with pulmonary hypertension. Also, QTc prolongation reported in another child was unlikely to be associated with nintedanib treatment as this event was reported 439 days after nintedanib discontinuation.

The risk for children under 6 years of age.

As nintedanib have not been studied in paediatric patients below 6 years old, (PDCO waiver) treatment of children below 6 years old with nintedanib is not recommended. The MAH considered that the contraindication for the use in small children is not justified and agreed by CHMP. Indeed, the risk of off-label use in children below 6 years it is considered to be low as the proposed indication (i.e. fibrosing interstitial lung diseases (ILDs)) is unlikely to be diagnosed in children below 6 years (based on the epidemiological data, as reflected in the chILD-EU Registry). Off label use in children younger than 6 years of age will monitored and discussed in each PSUR.

Long term safety data

The SmPC section 4.8 highlights that long term safety data in paediatric patients are not available and there are uncertainties on the potential impact on growth, tooth development, puberty, and the risk of liver injury. Of note, the extension trial is still ongoing, and this trial will provide further safety data in paediatric population.

Additional expert consultation

The AHEG was consulted for the following question:

The Experts are invited to provide their opinion on the overall safety profile of nintedanib when used in children and adolescents aged 6 to 17 years? Please consider the relevance of the observed effects on weight and potential risks in relation to growth, tooth development, and the risk of liver injury for children aged 6 to 11 and adolescents aged 12 to 17 years, respectively.

Summary:

All experts were of the opinion that the safety profile in children and adolescents from 6 to 17 years old is acceptable and manageable in this severely ill patient group. The experts highlighted the importance to closely monitor the safety in clinical practice with regards to the observed effects on weight, growth, tooth development and liver injury, also on long term use.

Some experts mentioned that the weight decrease was more of a concern due to the underlying nutritional issues in Childhood ILD patients and the fact that children are still growing compared to adult population. Among the experts, there was generally less concerns with bone/tooth development, liver injury. Monitoring safety concerns, regarding weight, bone, teeth and liver was considered of the same importance in both groups of patients from 6 to 11 years and from 12 to 17 years. It was also noted that the potential risks in relation to growth/bone and tooth development have been identified in preclinical studies and are also based on the mechanism of action of nintedanib.

The patients' representative mentioned that his daughter did not have any noticeable safety issues during the treatment. He mentioned also a decrease in appetite after stopping the treatment.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.9. Conclusions on clinical safety

The safety profile of nintedanib when used in adults is well known. AEs within the SOC gastrointestinal disorder such diarrhoea, nausea, abdominal pain and vomiting are most commonly reported. These very common ADRs were also seen in paediatric patients enrolled to the 1199-0337 and 1199-0378 trials. Weight decreased, decreased appetite, dehydration, bleeding (i.e. lower gastrointestinal haemorrhage, epistaxis heavy period), hepatic enzyme increased, headache which are common ADRs as per the SmPC were also reported in a small number of children.

Cases of drug-induced liver injury were reported in children exposed to nintedanib, though these cases had also confounding factors and none of these cases fulfilled the Hy's law criteria. The effect on liver in children will be further characterised in the extension study in the post marketing setting.

Uncommon ADRs or those with the frequency unknown (such hypertension, aneurysms and artery dissections, myocardial infarction, alopecia, renal failure and proteinuria) were not reported which is not unexpected due to the small number of exposed children (54 children exposed in both studies).

As already identified for adult population, nintedanib can cause weight decrease, and decreased appetite. 5 patients in the study had a significant decrease in body weight (>10%) which is concerning for children. Additional data on weight will be collected in trial 1199-0378.

Further, the use in children is associated with possible additional safety concerns not applicable to adults. Based on preclinical findings, there are possible "effects on tooth development" and "effect on bone development and growth". Although not confirmed based on the data available so far, these risks cannot be completely excluded taking into consideration the small number of exposed children to date, especially those younger than 12 years of age. These additional potential risks are listed in the RMP and are being further monitored in the ongoing extension study. There is a lack of long-term safety data in children. In addition, there are concerns in relation to the small number of paediatric patients enrolled studies. Of note, further data will be generated in the extension study.

In conclusion, the safety profile of nintedanib as observed in studies together with the planned pharmacovigilance activities (including additional data collection in the extension study) is acceptable.

2.7. Risk management plan

2.7.1. Safety concerns

Summary of safety concerns

Table 68: Summary of safety concerns in the agreed RMP

List of Important Risks and missing Information	
Important identified risks	DILI
	Bleeding
	Myocardial infarction
	Weight decreased in paediatric population
Important potential risks	Venous thromboembolism
	Arterial thromboembolism excluding myocardial infarction
	Perforation
	Hepatic failure
	Effect on bone development and growth in paediatric population
	Effect on tooth development and growth in paediatric population
Missing information	Treatment of SSc-ILD patients with pulmonary hypertension

List of important risks and missing information

Important identified risks	DILI
	Bleeding
	Myocardial infarction
	Weight decreased in paediatric population
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	Arterial thromboembolism excluding myocardial infarction
	Perforation
	Hepatic failure
	Effect on bone development and growth in paediatric population
	Effect on tooth development disorders in paediatric population
Missing information	Treatment of SSc-ILD patients with pulmonary hypertension

2.7.1.1. Conclusions on the safety specification

The safety specification as proposed by the MAH can be accepted.

2.7.2. Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

Table 69: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Trial 1199-0378 1199-0378 - (InPedILD™-ON) - An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease Ongoing	To assess the safety and tolerability of long-term treatment with nintedanib in paediatric patients with clinically significant fibrosing ILD	Effect on bone development and growth in paediatric population Effect on tooth development disorders in paediatric population	Final report	12 Jan 2026

2.7.3. Risk minimisation measures

Routine Risk Minimisation Measures

Table 70: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
DILI	*Routine risk communication* EU-SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation to investigate hepatic transaminase and bilirubin levels before treatment initiation and to monitor liver enzymes at regular intervals during treatment. Recommendation for dose reduction or treatment interruption as appropriate, and for permanent discontinuation if liver test elevations are associated with clinical signs or symptoms of liver injury. Recommendation to closely monitor patients with risk factors for elevation of liver enzymes. *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Bleeding	*Routine risk communication* EU-SmPC sections 4.4 and 4.8; PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.

Safety concern	Routine risk minimisation activities
Important identified risks (cont'd)	
Myocardial infarction	*Routine risk communication* EU-SmPC sections 4.4 and 4.8; PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Important potential risks	
Venous thromboembolism	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Arterial thromboembolism excluding myocardial infarction	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.

Safety concern	Routine risk minimisation activities
Important potential risks (cont'd)	
Perforation	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Hepatic failure	*Routine risk communication* EU-SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation to investigate hepatic transaminase and bilirubin levels before treatment initiation and to monitor liver enzymes at regular intervals during treatment. Recommendation for dose reduction or treatment interruption as appropriate, and for permanent discontinuation if liver test elevations are associated with clinical signs or symptoms of liver injury. Recommendation to closely monitor patients with risk factors for elevation of liver enzymes. *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.

Safety concern	Routine risk minimisation activities
Important potential risks (cont'd)	
Effect on bone development and growth in paediatric population	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation of regular monitoring of growth and evaluation of epiphyseal growth plate alteration via annual bone imaging in patients with open epiphyses. Recommendation for treatment interruption in patients who develop signs of growth impairment or epiphyseal growth plates alterations. *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indication.
Effect on tooth development disorders in paediatric population	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation of regular oral dental examination (at least every 6 months) until development of dentition is completed. *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indication.
Missing information	
Treatment of SSc-ILD patients with pulmonary hypertension	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.

Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

2.7.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 12.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable since the amendment of the product information remains limited and does not warrant a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Childhood interstitial lung disease (chILD) comprises a complex and heterogeneous spectrum of rare respiratory disorders, which affect infants, children, and adolescents and are associated with varying clinical course and prognosis. Currently, there are no approved therapies for the treatment of fibrosing ILD in children or adolescents.

The initially proposed indication was Treatment of fibrosis interstitial lung diseases (ILD). This proposal was further restricted during the course of the assessment. The agreed indications for nintedanib are ‘Treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs) and treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD) in children and adolescents from 6 to 17 years old’.

3.1.2. Main clinical studies

The clinical development programme to support the use of nintedanib in peadiatric ILD consists of a single, prospective Phase III clinical trial 1199-0337 (InPedILD). This submission contains also pooled analysis of efficacy results from trials 1199-0337 and 1199-0378. A focused pharmacokinetic (PK) and safety evaluation of nintedanib in paediatric patients in the age range of 6 to 17 years with clinically significant fibrosing ILD was performed in study 1199-0337. There was no primary efficacy endpoint in this study.

Due to the low prevalence of chILD, a basket approach, similar to the one used in the adult development programme for PF-ILDs other than IPF, was used in trial 1199-0337. It grouped together children and adolescents with different underlying clinical diagnoses of fibrosing ILDs (such as surfactant protein deficiency, cHP, toxic/radiation/drug-induced pneumonitis, SSc ILD, HSCT andconnective tissue disease related disorders) based on the claimed similarity in the pathophysiology of their disease in fibrotic remodelling. Supportive data on efficacy in the proposed paediatric programme were collected to support inferences of clinical benefit and evaluation of the benefit-risk of nintedanib in the target population.

Further to facilitate interpretation of the trial, additional statistical extrapolation analysis methods that leverage data collected in adults, including Bayesian analysis methods with informative priors, were provided.

3.1.3. *Favourable effects*

As the confirmatory efficacy trial in paediatric population was not performed the efficacy is mainly claimed based on the extrapolation from adults. A Bayesian dynamic borrowing approach, including a tipping point analysis, was applied to the treatment effect of nintedanib on FVC % predicted at Week 24 using a prior derived from adults and combining it with the analysis of paediatric data, using data from trial 1199-0337 only. Based on the results of Bayesian analysis, it is claimed that nintedanib is efficacious in paediatric patients with fibrosing ILD (median difference: 1.60, 95% credibility interval: -0.70, 3.09).

The 1199-0337 trial provides limited efficacy data on the use of nintedanib in children. Change from baseline in FVC % predicted at Weeks 24 and 52 was a secondary endpoint. For DBL2, at week 24, the adjusted mean difference between the treatment groups (nintedanib versus placebo) was 1.21 (95% CI -3.40, 5.81).

Some patients in the nintedanib group had an increase in FVC % predicted over 52 weeks in the study. As indicated by the MAH, at time of DBL2 for 4 patients (15.4%) in the nintedanib group FVC % had predicted increased by at least 5% (and less than 10%) from baseline to Week 24; 1 nintedanib patient (3.8%) had an absolute change from baseline of more than 10%. Following the 28 weeks of open-label nintedanib treatment (i.e. at Week 52), an increase from baseline in FVC % predicted of ≥5% to ≤10% was reported for 3 additional patients (1 patient in the nintedanib/nintedanib group and 2 patients in the placebo/nintedanib group).

Change from baseline in oxygen saturation (SpO2) on room air at rest at Weeks 24 and 52 was assessed as a secondary endpoint. The mean oxygen saturation of enrolled patients was 96.5% at baseline with lower value reported 85.0%. At week 24 it seems that patients on nintedanib maintained their oxygen saturation at rest whereas in patients on placebo there was some deterioration (adjusted mean of absolute change in oxygen saturation for nintedanib was 0.07 and for placebo was -2.25 at DBL2).

For adjusted mean (SE) of absolute change in PedsQLTM total score (parent assessment) from baseline to Week 24 there was no improvement. During the open-label period, the adjusted mean difference between treatment groups (nintedanib/nintedanib versus placebo/nintedanib) at Week 52 was 3.45 (95% CI -7.25, 14.16).

Slightly better results were reported for adjusted mean (SE) of absolute change in PedsQLTM total score (patient assessment). It is noted that for patient assessment, as opposite to the parent assessment, there was no further improvement in the open-label period.

The exercise capacity of patients was assessed using the change from baseline in 6-minute walk distance at Weeks 24 and 52. Based on data up to DBL2, the adjusted mean difference between the treatment groups was 7.2 m (95% CI -50.7 m, 65.0 m) at Week 24 and -(minus)-32.9 m (95% CI -103.1 m, 37.2 m) at Week 52.

As a supportive analysis, Bayesian dynamic borrowing approach, including a tipping point analysis, was applied to the treatment effect of nintedanib on FVC % predicted at Week 24 using a prior derived from adults and combining it with the analysis of paediatric data, using data from trial 1199-0337 only (median difference: 1.60, 95% credibility interval: -0.70, 3.09).

3.1.4. Uncertainties and limitations about favourable effects

Uncertainties and limitations linked to the extrapolation approach between adults and children

Differences in pathophysiological pathways of pulmonary fibrosis in children and adults have been noted (Nathan et al, 2019). At the cellular level, fibrosis in children is associated “with more inflammatory cell recruitment and less fibroblast recruitment and ECM deposition”. The treatment effect in children is likely to be similar or smaller (due to less fibroblast recruitment and ECM deposition) than that reported in adult patients with systemic sclerosis associated interstitial lung disease or with chronic fibrosing interstitial lung diseases with a progressive phenotype and other fibrosing patterns.

Uncertainties regarding diagnosis of clinically significant, progressive fibrosing interstitial lung diseases (ILDs)

There are more than 200 very rare different diseases included under a broad term “childhood ILDs”. Only a small proportion of children with childhood ILD (around 5%) develop clinically significant, progressive lung fibrosis. Further, there are no widely accepted radiologic or histopathologic criteria for identification of children with lung fibrosis and as well as for identification of progressive fibrosing phenotype in children. Therefore, there is a concern that due to diagnostic errors or unfamiliarity of physicians, children without progressive fibrosis could be treated with nintedanib. This concern was addressed by including a recommendation regarding the use of the multidisciplinary team in section 4.2 of the SmPC. Members of the AHEG strongly highlighted the need for a multidisciplinary team to be involved in the diagnosis and initiation of nintedanib treatment in children with fibrosing ILDs.

Limited data across the range of childhood interstitial lung diseases

Trial 1199-0337 enrolled patients with a spectrum of diseases. The most frequent single underlying ILD diagnoses were surfactant protein deficiency,systemic sclerosis and toxic/radiation/drug-induced pneumonitis. Chronic hypersensitivity pneumonitis was reported for 2 patients. The remaining underlying ILD diagnoses reported for 1 patient each. However, there are many other very rare diseases associated with progressive fibrosis which were not included in the paediatric studies performed by the MAH. For some of these diseases there are very limited literature data available. Therefore, section 4.4 of the SmPC highlights these limitations with the following statement: *Data on the use of nintedanib in paediatric patients is limited to a small subset of fibrosing interstitial lung diseases (see section 5.1). This subset does not cover all aetiologies associated with progressive fibrosing interstitial lung disease in paediatric patients.* The list of fibrosing interstitial lung diseases is included in section 5.1 of the SmPC.

Further, post-authorisation data collection on the use of nintedanib in children in the paediatric population is required particularly to describe the patient characteristics and the natural history of diseases not investigated in nintedanib studies or those represented in studies by one patient only.

The effect of other therapies

Although the use of other therapies was balanced between the groups, their effect on the treatment outcomes is difficult to determine taking into consideration the numbers of additional therapies given and the small number of children per group and ILD subtype. Therefore, uncertainty remains with regards to the contribution of the other therapies in the effect observed with nindetanib.

3.1.5. Unfavourable effects

At the pooled analysis, at least 1 treatment-emergent AE during the nintedanib-exposure period of trials 1199-0337 and 1199-0378 was reported 100% of children. SAEs were reported in 15 (27.8 %) children including 8 in the extension study, drug-related AEs were reported in 39 (72.2%) children (27 in the extension study) and AEs leading to discontinuation in 3 children (1 new event reported in the extension study).

The safety profile of nintedanib when used in adults is well known. AEs within the SOC gastrointestinal disorder such diarrhoea, nausea, abdominal pain and vomiting are most commonly reported. These very common ADRs were also seen in paediatric patients enrolled to the 1199-0337 and 1199-0378 trials. Weight decreased, decreased appetite, dehydration, bleeding (i.e. lower gastrointestinal haemorrhage, epistaxis heavy period), hepatic enzyme increased, headache which are common ADRs as per the SmPC were also reported in a small number of children.

Cases of drug-induced liver injury were reported in children exposed to nintedanib, though these cases had also confounding factors and none of these cases fulfilled the Hy's law criteria. The effect on liver in children will be further characterised in the extension study in the post marketing setting.

Uncommon ADRs or those with the frequency unknown (such hypertension, aneurysms and artery dissections, myocardial infarction, alopecia, renal failure and proteinuria) were not reported which is not unexpected due to the small number of exposed children (54 children exposed in both studies).

As already identified for adult population, nintedanib can cause weight decrease, and decreased appetite. 5 patients in the study had a significant decrease in body weight (>10%) which is concerning for children. Additional data on weight will be collected in trial 1199-0378.

Further, the use in children is associated with possible additional safety concerns not applicable to adults. Based on preclinical findings, there are possible "effects on tooth development" and "effect on bone development and growth".

These risks cannot be completely excluded taking into consideration the small number of exposed children to date, especially those younger than 12 years of age. These additional potential risks are listed in the RMP and are being further monitored in the ongoing extension study. There is a lack of long-term safety data in children. In addition, there are concerns in relation to the small number of paediatric patients enrolled studies. Of note, further data will be generated in the extension study.

In conclusion, the safety profile of nintedanib as observed in studies together with the planned pharmacovigilance activities (including additional data collection in the extension study) is acceptable.

3.1.6. Uncertainties and limitations about unfavourable effects

There are concerns in relation to the small number of paediatric patients enrolled in studies and the therefore limited paediatric exposure to nintedanib leading to uncertainties regarding the safety profile of nintedanib when used in children especially for younger patients (6 to 12 years of age) as only 17 patients were enrolled within this age category.

Effects on growth and tooth development

Reversible epiphyseal growth plate alterations were observed in preclinical studies and therefore radiological and growth assessments were performed in trials 1199-0337 and 1199-0378. At week 52 of 1199 0337 trial there were 5 patients treated with nintedanib with pathological findings on the epiphyseal growth plate on imaging. These changes were also seen at baseline or resolved later while on treatment. An additional AE of growth plate disorder in a patient treated with nintedanib was

reported during the double-blind period. This pathological finding, however, was not confirmed by the central review as it was considered that the status of epiphyseal closure was open.

Drug-induced liver injury

cases of drug-induced liver injury have been observed with nintedanib treatment in adults, including severe liver injury with fatal outcome; therefore, children are at risk of developing such severe events as well.

Liver abnormalities (including liver injury, hepatitis and one case of DILI) were reported in children, although none of the patients reported with a hepatic event fulfilled the Hy's law criteria of ALT and/or AST elevations ≥3x ULN concurrent with an elevation in total bilirubin ≥2x ULN. In a single case the hepatic event associated with abdominal pain led to treatment discontinuation. In the other cases the hepatic event resolved and treatment with nintedanib could be continued. The risk of DILI in the paediatric population will be closely monitored in the post-marketing setting and it will be discussed routinely in the PSURs.

Of note, DILI is listed as an important identified risk and hepatic failure is listed as an important potential risk in the RMP.

There are no long-term safety data available at present.

3.1.7. Effects Table

Table 71: Effects Table for Ofev for the treatment of fibrosing Interstitial Lung Diseases (ILDs) and SSc-ILDs in children and adolescents from 6 to 17 years of age

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change in FVC % predicted- upto DLP2 (week 52)	Change from baseline in FVC % predicted at Week 24 and 52		1.25 (-1.08, 3.57)	0.34 (-2.98, 3.67)	Nintedanib versus placebo Adjusted mean 1.21 (95% CI -3.40, 5.81)	
Bayesian analysis incorporating data from previous clinical trials in adult patients with fibrosing ILDs Change in FVC % predicted	Change from baseline in FVC % predicted at Week 24	Median difference of 1.63 (nintedanib compared with placebo; 95% credible interval: -0.69 to 3.40				

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Diarrhoea double-blind period u to DBL2		N(%)	10 (38.5)	2 (15.4)		1199-0337 trial
Hepatobiliary and liver laboratory organ system AEs		N(%)	3 (11.5)	0	Liver abnormalities (i.e. liver injury, hepatitis or asymptomatic increase in liver enzymes) were reported 10 children treated with nintedanib in trials 1199 0337 and 1199 0378.	trials 1199-0337 and 1199 0378.
Stunted growth of the dental root Decreased weight		N(%)	6 (23.1)	0	5 patients treated with nintedanib with pathological findings on the epiphyseal growth plate on imaging.	trials 1199-0337 and 1199-0378.

3.1.8. Benefit-risk assessment and discussion

Childhood interstitial lung disease (chILD) comprises a complex and heterogeneous spectrum of rare respiratory disorders, which affect infants, children, and adolescents and are associated with varying clinical course and prognosis. It is important to note that the fibrotic pattern is very likely to have an impact on efficacy.

Currently, there are no approved therapies for the treatment of fibrosing ILD in children or adolescents and therefore there is an unmet medical need.

As a confirmatory efficacy trial in the paediatric population was not performed, the efficacy is claimed based on extrapolation from adults. While recognizing uncertainties to this approach, the CHMP considered that extrapolation of efficacy from adults with systemic sclerosis associated ILD and chronic fibrosing ILDs with a progressive phenotype (other than IPF and those with UIP pattern) to children aged 6 to 17 years with systemic-sclerosis associated ILD and progressive, or clinically significant fibrosing interstitial lung disease can be accepted; also taking into account the input provided by the AHEG.

The proposed target population initially applied was considered too broad as it may also include children who will not progress with fibrosis and/or who could respond to the standard therapies. Therefore, the indication was updated as follows: *Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs) (see section 4.2 and 5.1)*.

As systemic sclerosis associated interstitial lung disease (SSc-ILD) is diagnosed both in adults and children it is was considered acceptable to extrapolate results in the paediatric population and accept the indication in adolescents and children aged 6 years and older for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

The absence of widely accepted radiologic or histopathologic criteria for identification of children with lung fibrosis and as well as for identification of progressive fibrosing phenotype in children may induce diagnostic errors that children without progressive diagnosis may be treated with nindetanib. This concern has been addressed by including a recommendation regarding the use of the multidisciplinary team in section 4.2 of the SmPC.

The safety profile was generally similar in paediatric patients compared to the adult population. However, additional potential safety concerns in the paediatric population that are not applicable to adults were also observed as follows: the effect on bone development and growth and effect on tooth development disorders. These effects are included as important potential risks in the RMP. These risks will be monitored in the post marketing as a part of the safety assessment in the ongoing extension study and through the routine pharmacovigilance.

The SmPC highlights uncertainties in relation to the effect on growth and tooth development. Section 4.8 of the SmPC states: *Long term safety data in paediatric patients are not available. There are uncertainties on the potential impact on growth, tooth development, puberty, and the risk of liver injury*.

It is important to note that due to the small number of paediatric patients enrolled in studies, and the therefore limited paediatric exposure to nintedanib, uncertainties regarding the safety profile of nintedanib when used in children remain which will be characterized post approval.

Finally, long term safety data are not yet available for children.

3.1.9. Balance of benefits and risks

The extrapolation from adult diseases presenting with other fibrosing pattern (such as fibrotic NSIP) is considered justified for the following groups of children aged 6 years and older: clinically significant, progressive fibrosing interstitial lung diseases (ILDs) and systemic sclerosis associated interstitial lung disease (SSc-ILD).

The CHMP decision was supported by the consultation of an ad-Hoc Expert Group meeting. The members of the AHEG highlighted the need for a multidisciplinary team to be involved in the diagnosis and initiation of nintedanib treatment in children with fibrosing ILDs, which is implemented in section 4.2 of the SmPC.

In order to address limitations due to the rarity of the disease and available limited clinical data, upon request of CHMP, the MAH committed to conduct post-authorisation data collection (legally binding measure) on the use of nintedanib in children in the paediatric population, e.g. through an appropriate EU registry (as currently done for the adult population with systemic sclerosis associated ILD and chronic fibrosing ILD with a progressive phenotype).

The aim of this collection of data will be to describe the patient characteristics and the natural history of diseases not investigated in nintedanib studies. The safety profile will be further characterized by the post authorisation data collection and the currently ongoing extension study 1199-0378.

3.1.10. Additional considerations on the benefit-risk balance

N/A

3.2. Conclusions

The overall benefit/risk balance of nintedanib in the proposed indication is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ofev 25 mg is favourable in the following indications:

Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant, progressive fibrosing interstitial lung diseases (ILDs) (see section 4.2 and 5.1).

Ofev is indicated in adolescents and children aged 6 years and older for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Ofev subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		Type	Annexes affected
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension application to add a new strength of 25 mg hard capsules, grouped with an extension of indication (C.I.6.a) in children and adolescents from 6 to 17 years of age. This is based on results from study 1199-0337 (double-blind, randomised, placebo-controlled trial) in paediatric patients from 6 years of age with clinically significant progressive fibrosing Interstitial Lung Disease to evaluate the dose-exposure and safety of nintedanib on top of standard of care for 24 weeks, followed by open label treatment supplemented by an ongoing prospective Phase III extension trial 1199-0378 over at least 2 years. Consequently sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.1, 6.3, 6.4 and 6.5 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 12.3 of the RMP has also been agreed.