Clinical Trial Protocol

	Document Number:	**c26450188-03**
EudraCT No. **EU Trial No.**	2018-004530-14	
BI Trial No.	1199-0337 (InPedILD™)	
BI Investigational Medicinal Product(s)	Ofev®, nintedanib	
Title	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	
Lay Title	A study to find out how nintedanib is taken up in the body and how well it is tolerated in children and adolescents with Interstitial Lung Disease (ILD)	
Clinical Phase	III	
Clinical Trial Leader	[redacted] Phone: +[redacted] Fax: +[redacted]	
Coordinating Investigator	[redacted] Phone: +[redacted] Fax: +[redacted]	
Status	Final Protocol (Revised Protocol based on Global Amendment 2)	
Version and Date	**Version: 3.0**	**Date: 14 Jun 2021**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	09 Jul 2019
Revision date	14 Jun 2021
BI trial number	1199-0337
Title of trial	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
Coordinating Investigator	[redacted]
Trial sites	Multi-centre trial conducted in approximately 24 countries.
Clinical phase	III
Trial rationale	Some patients with childhood interstitial lung disease (chILD) develop chronic lung fibrosis similar to adults with fibrosing lung disease, which is associated with significant morbidity and mortality. There are currently no approved therapies for the treatment of fibrosing interstitial lung disease in children. Based on the presumed similarities in underlying pathophysiology resulting in fibrotic remodelling in adults and children, it is postulated that matching the dose exposure of nintedanib in children will lead to similar anti-fibrotic effects and clinical benefits in paediatric patients with fibrosing lung disease as demonstrated in adults with IPF and SSc-ILD. As a powered efficacy study is not feasible, a focused pharmacokinetic (PK) and safety evaluation of nintedanib in children with clinically significant chronic fibrosing lung disease is planned to determine appropriate paediatric dosing of nintedanib in children and adolescents and to address this unmet need.
Trial objective(s)	The main objective of the study is to evaluate dose-exposure and safety of nintedanib in children and adolescents with fibrosing ILD.
Trial endpoints	Primary endpoints: • PK: AUCτ,ss based on sampling at steady state (at week 2 and week 26); • N (%) of patients with treatment-emergent adverse events at week 24. Secondary endpoints:

	• N (%) of patients with treatment-emergent pathological findings of epiphyseal growth plate on imaging at week 24, and week 52*; • N (%) of patients with treatment-emergent pathological findings on dental examination or imaging at week 24, and week 52*; • N (%) of patients with treatment-emergent adverse events over the whole trial; • Change in height, sitting height, leg length from baseline at week 24, week 52*, week 76*, and week 100*. • Change in Forced Vital Capacity (FVC) % predicted from baseline at week 24, and week 52*; • Absolute change from baseline in Pediatric Quality of Life Questionnaire™ (PedsQL™) at week 24, and week 52*; • Change in oxygen saturation (SpO_2) on room air at rest from baseline at week 24, and week 52*. • Change in 6-min walk distance from baseline at week 24, and week 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 hospitalization over the whole trial; • Time to first acute Interstitial Lung Disease (ILD) exacerbation or death over the whole trial; • Time to death over the whole trial; *52 weeks, 76 weeks, 100 weeks time points will not be available for all patients.
Trial design	Double blind, randomised, placebo-controlled on top of standard of care (SOC) over 24 weeks, followed by open label active treatment of variable duration.
Total number of patients randomised	At least 30 randomised patients including at least 20 adolescents aged 12-17 years.
Number of patients on each treatment	Nintedanib: approx. 20* Placebo: approx. 10* *Patients will be allocated to the treatments in a ratio of 2:1 (Nintedanib:Placebo).
Diagnosis	Clinically significant fibrosing Interstitial Lung Disease
Main in- and exclusion criteria	Main inclusion criteria: Male or female 6 to 17 years old at Visit 2, with evidence of fibrosing ILD on HRCT within 12 months of Visit 1, FVC % predicted ≥25% at Visit 2 and clinically significant disease at Visit 2 based on either clinical markers of disease severity or evidence of clinical progression over time.

	Main exclusion criteria: AST and/or ALT and/or bilirubin >1.5 x ULN, and/or creatinine clearance <30 mL/min (Schwartz formula), and/or 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 is shorter but ≥1 week) prior to Visit 2; significant pulmonary arterial hypertension, any cardiovascular disease excluded by protocol, history of thrombotic event within 12 months of Visit 1, other disease that may interfere with testing procedures or trial participation, or may put the patient at risk; bleeding risk; life expectancy for any concomitant disease other than ILD <2.5 years (investigator assessment); any diagnosed growth disorder or any genetic disorder associated with short stature and/or treatment with growth hormone therapy within 6 months before Visit 2; <13.5 kg of weight at Visit 1.
Test product(s)	Nintedanib
dose	Starting dose assigned based on patient's weight at Visit 2: 150 mg b.i.d. (300 mg daily), 100 mg b.i.d. (200 mg daily), 3x25 mg b.i.d. (150 mg daily), 2x25 mg b.i.d. (100 mg daily). During treatment dose is adjusted based on patient's weight. Dose reduction to the next lower dose is possible to manage adverse events. The lowest possible dose is 25 mg b.i.d. (50 mg daily).
mode of administration	Per os
Comparator product(s)	Placebo
dose	Not applicable
mode of administration	Per os
Duration of treatment	24 weeks of double blind, randomised, placebo-controlled treatment on top of SOC (Part A), followed by open label active treatment of variable duration (Part B). During Part B patients will continue treatment with nintedanib on top of SOC until the end of the trial (i.e. the date of the last visit of the last patient in the whole trial) or premature discontinuation. Patients who completed the treatment period according to protocol will be offered participation in a separate open label extension trial. The open label extension trial will be initiated if supported by the benefit-risk assessment from DBL 1 of the current trial.
Statistical methods	Descriptive statistics will be provided for PK and safety endpoints. Analysis of secondary endpoints will be descriptive in nature using a mixed model with repeated measurements (MMRM) for continuous endpoints. Time-to-event endpoints will be displayed descriptively using the Kaplan-Meier method. Categorical endpoints, safety and tolerability will be displayed descriptively in frequency tables.

FLOW CHART

Trial Periods	**Screening**		**Treatment***														**Follow-up**
			Randomised Part A					**Open label Part B**									
Visit		**1**	**2**	**3**	**4**	**5**	**5a**	**6**	**7**	**7a**	**8**	**8a**	**9**	**9a**	**X**	**Xa**	**EoT ******	**EoTrial *******
Weeks******		-4	0	2	6	12	as needed	24	26	as needed	36	as needed	52	as needed	52 plus Q12w	as needed		
Days****** Time window for visits (days)	Before or at the latest at Visit 1	≤28d before Visit 2	D 1 **** none	15 ±3	43 ±3	85 ±3	na	169 ±3	183 ±3	na	253 ±7	na	365 ±7	na	365 plus Q84d ±7	na		EoT plus 28 days +3
Informed consent and assent[1]	X																	
HRCT sent to central review[2]	X																	
Biopsy sent to central review (if required)[2]	X																	
Demographics		X																
Medical history		X																
Physical examination, Vital signs[3]		X	X	X	X	X		X	X		X		X		X		X	X
Height (standing and sitting)[4]		X	X			X		X			X		X		X		X	(X)
Leg length			X			X		X			X		X		X /Q24w		X	

Trial Periods	**Screening**		**Treatment***														**Follow-up**
			Randomised Part A					**Open label Part B**									
Visit		**1**	**2**	**3**	**4**	**5**	**5a**	**6**	**7**	**7a**	**8**	**8a**	**9**	**9a**	**X**	**Xa**	**EoT ******	**EoTrial *******
Weeks******		-4	0	2	6	12	as needed	24	26	as needed	36	as needed	52	as needed	52 plus Q12w	as needed		
Days****** Time window for visits (days)	Before or at the latest at Visit 1	≤28d before Visit 2	D 1 ******** none	15 ±3	43 ±3	85 ±3	na	169 ±3	183 ±3	na	253 ±7	na	365 ±7	na	365 plus Q84d ±7	na		EoT plus 28 days +3
Weight[4]		X	X	X	X	X		X			X		X		X		X	(X)
12 lead-ECG (at rest)[5]		X	(X)					X					X		X /Q24w		X	
Laboratory tests[6,7,8]		X[7]	X	X	X	X	(X)	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)
Pregnancy tests[9]		X	X	X	X	X		X	X		X		X		X		X	X
Review with patient and dispense pregnancy test diary card together with urine dipstick pregnancy test (if applicable)[9]					X	X		X	X		X		X		X		X	
[redacted]																		
SpO_2 (room air, resting)		X	X	X	X	X		X	X		X		X		X		X	
FVC[11]		X	X	X	X	X		X	X		X		X		X		X	
D_{LCO}[11]			X															
Fan severity score			X															
Review of in-/ exclusion criteria		X	X															

Trial Periods	**Screening**		**Treatment***															**Follow-up**
			Randomised Part A					**Open label Part B**										
Visit		**1**	**2**	**3**	**4**	**5**	**5a**	**6**	**7**	**7a**	**8**	**8a**	**9**	**9a**	**X**	**Xa**	**EoT ******	**EoTrial *******
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Days****** Time window for visits (days)	Before or at the latest at Visit 1	≤28d before Visit 2	D 1 ******** none	15 ±3	43 ±3	85 ±3	na	169 ±3	183 ±3	na	253 ±7	na	365 ±7	na	365 plus Q84d ±7	na		EoT plus 28 days +3
IRT call/ notification	X[12]		X	X	X	X		X[12]			X		X		X		X	
Randomisation			X															
Administer trial drug			X	X				X	X									
Dispense PK diary card[13]			X					X										
PK Sampling[13]				X					X									
Dispense trial drug			X	X	X	X		X			X		X		X			
Collect trial drugs				X	X	X		X			X		X		X		X	
Compliance check/ drug accountability				X	X	X		X	X[14]		X		X		X		X	
Criteria for dose reduction/ interruption check				X	X	X		X	X		X		X		X		X	
Acceptability questionnaire				X				X										
PedsQL™[15]			X					X					X					
6MWT, Borg CR-10 scale®, SpO_2			X					X					X					

Trial Periods	**Screening**		**Treatment***														**Follow-up**
			Randomised Part A					**Open label Part B**									
Visit		**1**	**2**	**3**	**4**	**5**	**5a**	**6**	**7**	**7a**	**8**	**8a**	**9**	**9a**	**X**	**Xa**	**EoT ******	**EoTrial *******
Weeks******		-4	0	2	6	12	as needed	24	26	as needed	36	as needed	52	as needed	52 plus Q12w	as needed		
Days****** Time window for visits (days)	Before or at the latest at Visit 1	≤28d before Visit 2	D 1 ******** none	15 ±3	43 ±3	85 ±3	na	169 ±3	183 ±3	na	253 ±7	na	365 ±7	na	365 plus Q84d ±7	na		EoT plus 28 days +3
[redacted]																		
ILD exacerbations			X	X	X	X		X	X		X		X		X		X	X
Hospitalizations (respiratory-related)			X	X	X	X		X	X		X		X		X		X	X
Bone imaging (if applicable)[16]			X			X		X			X		X		X /Q24w		X	
Dental examination[16]			X			X		X			X		X		X /Q24w		X	
Dental imaging[16]			X					X					X		X /Q48w		X	
All AEs/ SAEs/AESIs[17]	X	X	X	X	X	X		X	X		X		X		X		X	X
Concomitant therapy		X	X	X	X	X		X	X		X		X		X		X	X
Completion of patient participation																		X
Vital status data[18]								X					X					X

(*) In case of dose change (reduction or re-escalation) additional visits have to be included.

(**) Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EoT) visit as soon as possible, and follow the trial schedule thereafter, if possible. The patient will be asked to attend all visits (except for the laboratory a-visits) as originally planned until the end of the trial. Please also see Flow Chart footnote 18 for instructions, should the patient be unable to complete the scheduled visits; see Section 6.2.3 for details on trial procedures at these visits.
The first visit after the EoT visit will be skipped if the EoT visit occurs within 4 weeks prior to scheduled visit.
Patients who did not discontinue trial treatment prematurely should undergo the EoT visit as soon as the timing of final DBL (DBL 2) and EoT visit has been communicated (see Section 3.1 for details). If a regular study visit is scheduled in the period when the EoT visit should be conducted, all procedures required at this regular study visit and the additional procedures, if any, required at the EoT visit will be conducted during the same visit.

(***) After the EoT visit, patients who completed the treatment period according to protocol will enter a 4-week follow-up period, unless they roll-over into an open label extension trial. See Section 3.1 for details.

(****) Weeks and Days from the Day of Randomisation, i.e. Day of first intake of randomised medication (D 1).

[1]Informed consent (and assent where applicable) will be obtained before any procedure related to the study. When it is obtained before Visit 1, e.g. to allow shipment of images for central review, all Adverse Events (AEs) and Concomitant Treatments occurring after the informed consent have to be recorded, including those occurred between informed consent and Visit 1. The interval between Visit 1 and Visit 2 should be ≤28 days. The interval between Visit 1 and Visit 2 could be >28 days in case the assessments required to check inclusion and exclusion criteria cannot be completed within 28 days (e.g. in case the available HRCT scan fails to meet the required image acquisition specification, laboratory test results show out-of-range values requiring retest, etc.) but the screening period (informed consent to Visit 2) must not be longer than 12 weeks. Upon obtaining informed consent, the patient and parent(s)/legal guardian will be instructed on procedures to be followed until the next study visit.

[2]Central review of high resolution computed tomography (HRCT) for meeting inclusion criteria. HRCT should not be older than 12 months. If the patient does not have a HRCT within 12 months of Visit 1 or the available HRCT scan fails to meet the required image acquisition specification (see image acquisition guideline in the ISF), a new HRCT can be performed for the purposes of participation in the trial, provided the patient meets all other in-/exclusion criteria. For details about HRCT and biopsy review see Section 3.3.2.1.

[3]Measurements of vital signs should precede blood sampling; except at Visit 3 and Visit 7 (as blood sampling for PK will start upon patient's arrival).

[4]At each time point, height and sitting height will be assessed three times and each assessment will be recorded into the patient's files and transcribed into the electronic Case Report Form (eCRF). An average of the 3 measurements will be calculated. Height and weight will be repeated at follow-up in case of clinically relevant changes at EoT. Height and weight assessed in the 2 years prior to screening (Visit 1) will also be collected, if available.

[5]Electrocardiogram (ECG) at rest (if possible prior to blood sampling) will be performed at Visit 1. It will be repeated at Visit 2 prior to randomization only if abnormal at Visit 1, and at visits specified in the Flow Chart thereafter.

[6]Safety laboratory tests will be conducted on blood and urine. Tests will be repeated at follow-up (unless patients roll-over into the open label extension trial) in case of clinically relevant changes at EoT.

[7]The safety laboratory tests of Visit 1 must be repeated if screening is longer than 6 weeks.

[8]Intermediate lab tests ("a" Visit) will be done as needed for additional safety monitoring at the discretion of the investigator, or as recommended by the Safety Monitoring Committee (SMC). Laboratory kits for blood and urine sampling done locally (e.g. by the general practitioner or a nurse) and for shipping to central laboratory will be provided. Analyses will be conducted by central laboratory.

[9]Beta-Human Chorionic Gonadotropin (HCG) testing will be conducted in all female patients, even pre-menarche, on blood collected at each scheduled visit until EoT. Pregnancy testing should be repeated every 4-6 weeks, i.e. at least at every visit and additionally at home or at a local laboratory / local doctor from Visit 4 until the end of the trial. If urine test is not acceptable to local authorities, a blood test will be done at a local laboratory. If applicable, urine dipstick pregnancy tests will be dispensed from Visit 4 until EoT, and use of pregnancy test diary card will be explained with the patient and/or parent(s)/legal guardian. Retuned diary card will be reviewed with patient or parent(s)/legal guardian from Visit 5 until EoT, and training will be repeated as needed. The pregnancy test diary card will be used to support the record of the date and result of test(s) between consecutive visits. At the Follow-up Visit the pregnancy test will be conducted on urines (if acceptable), and test results will be documented in the patient's records. In case a positive test is reported the sponsor should be contacted immediately. Refer to Section 3.3.4.1 for further instructions. Refer to Section 5.2.7.2.3 for detailed information on event reporting in case of pregnancy.

[redacted]

[11]Order of lung function measurements at Visit 2: 1. FVC followed by patient's rest; 2. D_{LCO}. After Visit 2 FVC measurements to be done at approximately the same time each visit, with reference time at Visit 2.

[12]Interactive Response Technology (IRT) should be notified upon obtaining informed consent, at Visit 1 at the latest. At Visit 6 IRT will assign open label treatment, and Part B will start once the first open label dose has been taken in the morning during the visit.

[13]PK samples will be taken before drug administration at the clinic and at 6 timepoints post-dose (see Flow Chart for PK blood sampling for details). In exceptional cases, where extensive PK sampling is not possible and only in paediatric patients with an age < 12 years, a sparse sampling approach might be applied with a minimum blood sampling before (PTM of -0:05), 1 h (+/- 15 min) and 3 h (+/- 15 min) after nintedanib administration. Date and exact clock time of drug administration and blood sampling must be recorded in the eCRF. The patient and parent(s)/legal guardian will be provided (Visit 2 and Visit 6) with a PK diary card to support the record of the exact clock time of medication intake on the three days preceding PK sampling. At the beginning of the PK sampling visit (Visit 3 and Visit 7) the site personnel will check the PK diary card and confirm that the trial medication has been taken in the three days preceding the visit. If this is not confirmed, the visit will be rescheduled.

[14]At this visit drug accountability is to be completed only in case of dose reduction / increase.

[15]The PedsQL™ questionnaire should always be administered in a quiet place prior to any other visit procedure.

[16]Bone imaging (Magnetic Resonance Imaging (MRI) examination; if MRI cannot be performed, x-ray assessment) will be conducted in all patients who qualified for randomisation at baseline. Imaging follow-up will be conducted only in patients with open physes at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter until the end of the study or closure of the physes. At EoT the MRI/x-ray should not be repeated if the last MRI/x-ray was conducted within 12 weeks in the first year, 24 weeks thereafter.

Dental examination (clinical) will be conducted in all patients who qualified for randomisation at baseline. Follow-up will be conducted in all patients at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter until the end of the study. At EoT the dental examination will not be repeated if the last examination was conducted within 12 weeks.

Dental imaging (panoramic x-ray) will be conducted in all patients who qualified for randomisation at baseline. Follow-up will be conducted in all patients at 24 weeks, 52 weeks and every 48 weeks thereafter until the end of the study. At EoT the dental imaging should not be repeated if the last dental imaging was conducted within 24 weeks.

If it's not possible to conduct the baseline bone imaging, and/or dental examination, and/or dental imaging on the day of Visit 2, the procedure can be done in the 2 weeks (until study day 15) immediately after the visit. If it's not possible to conduct the follow-up bone imaging, and/or dental examination, and/or dental imaging on the day of the visit, the procedure can be done in the week immediately before or after the visit. Please refer to the image acquisition guideline available in the ISF for details.

[17]After the individual patient's end of the trial the investigator should report only any occurrence of cancer, study treatment related Serious Adverse Events (SAEs) and study treatment related Adverse Event of Special Interests (AESIs) of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form, but not on the eCRF. Please see Section.5.2.7.2.1.
[18]Patients who prematurely discontinue trial medication will be asked to remain in the study and return to all regularly scheduled visits until the end of the trial. For those patients who are unable to complete the scheduled visits, every attempt will be made to get information on vital status at 24 weeks after randomization, i.e. the time of the data cut-off for the primary analysis of safety, at 52 weeks and at the end of the trial.

In the event of force majeure or other disruptive circumstances (e.g. pandemic) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient's parent(s)/legal guardian (and assent by the patient where applicable), sponsor and investigator may implement risk mitigation measures and modifications to CTP standard procedures as described in Appendix 10.9. See also Section 4.1.4, Section 6.1 and ISF for details.

FLOW CHART FOR PK BLOOD SAMPLING

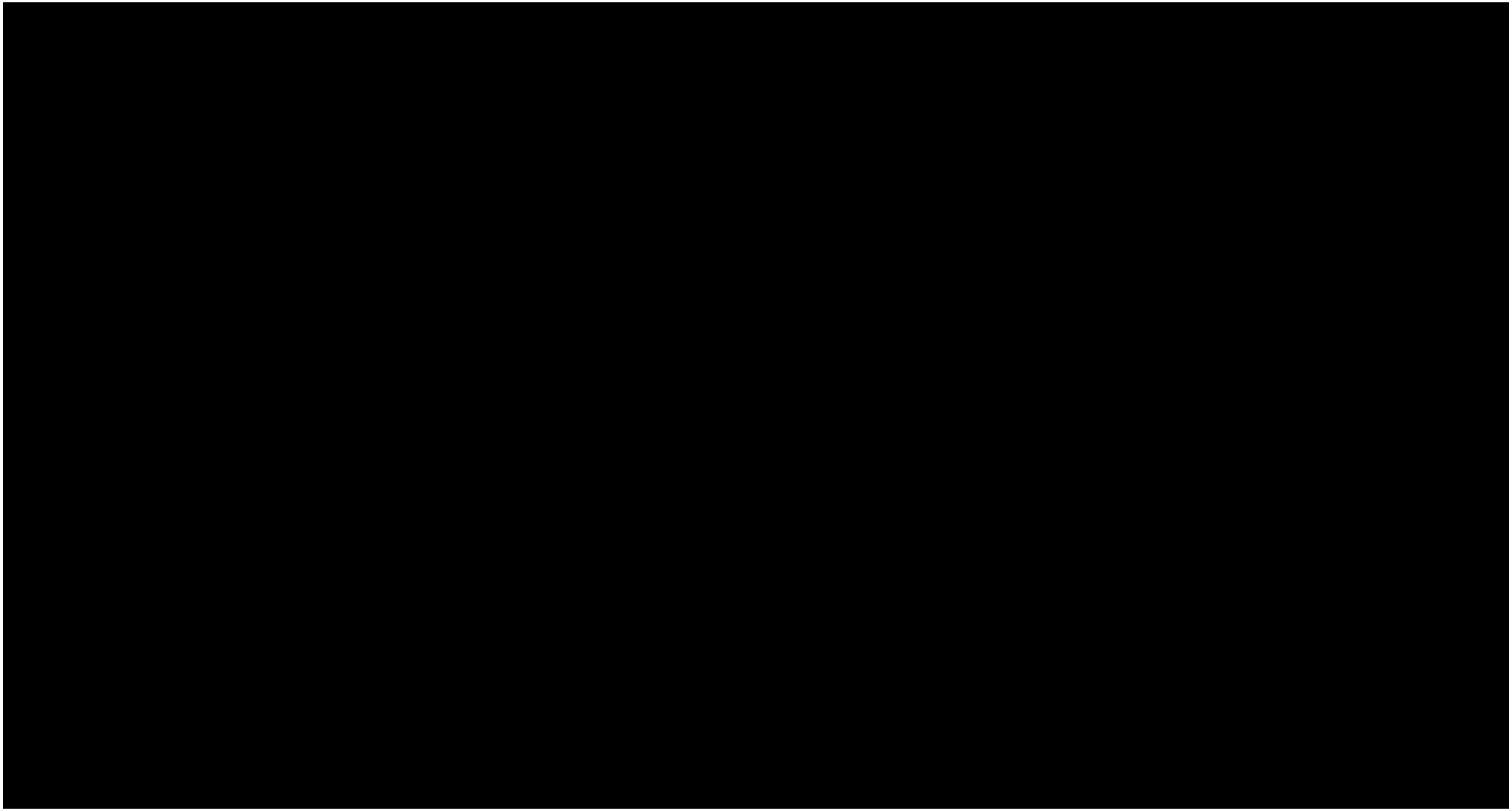
Visit	Week (±days)	Time Point [hh:min]	CRF Time /PTM	Event
3 (Part A)	2 (±3)	-0:05[1]	-0:05	PK Blood
		0:00	---	Drug administration
		1:00[2]	1:00	PK Blood
		2:00[2]	2:00	PK Blood
		3:00[2]	3:00	PK Blood
		4:00[3]	4:00	PK Blood
		6:00[3]	6:00	PK Blood
		8:00[3]	8:00	PK Blood
7 (Part B)	26 (±3)	-0:05[1]	-0:05	PK Blood
		0:00	---	Drug administration
		1:00[2]	1:00	PK Blood
		2:00[2]	2:00	PK Blood
		3:00[2]	3:00	PK Blood
		4:00[3]	4:00	PK Blood
		6:00[3]	6:00	PK Blood
		8:00[3]	8:00	PK Blood

[1]Upon patient's arrival at the clinic, just before drug administration.
[2]Time window for 1:00, 2:00 and 3:00 hour post-dose PK sampling: +/-15 min.
[3]Time window for 4:00, 6:00 and 8:00 hour post-dose PK sampling: +/-30 min.

Extensive blood sampling will be done for the primary PK analysis. In exceptional cases of paediatric patients aged <12 years, where extensive PK sampling is not possible, a sparse sampling approach should be applied with a minimum blood sampling before (PTM of -0:05) and 1 h (+/- 15 min) as well as 3 h (+/- 15 min) after nintedanib administration.

In rare circumstances PK sampling might need to be repeated (e.g. blood samples not taken at required timepoint, wrong medication taken in the days before PK sampling or on the day of PK sampling, destroyed/lost sample during shipment). In such cases PK sampling will be repeated close before the end of treatment visit, to allow the maximum possible interval from the previous PK sampling.

A total blood volume of 1.2 mL per time point is required.



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ABBREVIATIONS

ABCA3	ATP Binding Cassette Subfamily A Member 3
AC	Adjudication Committee
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Antero Posterior
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
ATS / ERS	American Thoracic Society / European Respiratory Society
$AUC_{\tau,ss}$	Area under the Plasma Concentration-Time Curve at Steady State
b.i.d.	bis in die (twice daily dosing)
ß-HCG	Beta- Human Chorionic Gonadotropin
[redacted]	
Beta-HCG	Beta- Human Chorionic Gonadotropin
BI	Boehringer Ingelheim
BLQ	Below the Limit of Quantification
CA	Competent Authority
chILD	Childhood Interstitial Lung Disease
cHP	Chronic Hypersensitivity Pneumonitis
CL/F_{ss}	Apparent Clearance of the Analyte in the Plasma at Steady-State following extravascular multiple dose administration
CK	Creatine Kinase
C_{max}	Maximum Concentration in Plasma
$C_{max,ss}$	Maximum Measured Concentration of the Analyte in Plasma at Steady State
CNS	Central Nervous System
COHb	Carboxyhaemoglobin
COVID-19	Coronavirus Disease 2019
$C_{pre,ss}$	Predose Concentration of the Analyte in Plasma at Steady State immediately before administration of the next dose
CRA	Clinical Research Associate

CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRA	Contract Research Associate
CRO	Contract Research Organisation
CSF1R	Colony-Stimulating Factor 1 Receptor
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4
Δ	Delta, i.e. difference
d	Day(s)
DBL	Database Lock
DILI	Drug Induced Liver Injury
D_{LCO}	Diffusing Capacity of the Lung for Carbon Monoxide
DM	Dermatomyositis
DRC	Disease Review Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EDTA	Ethylenediamine-Tetraacetic Acid
EoT	End of Treatment
EoTrial	End of Trial
EudraCT	European Clinical Trials Database
FC	Flow Chart
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FPE	First Patient Enrolled
FPI	First Patient In
FUP	Follow-up
FVC	Forced Vital Capacity

GCP	Good Clinical Practice
gCV	Geometric Coefficient of Variation
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastro-Intestinal
GLI	Global Lung Initiative
GMP	Good Manufacturing Practice
h	hour
HA	Health Authority
[redacted]	
Hb	Haemoglobin
Hct	Haematocrit
HP	Hypersensitivity Pneumonitis
HRCT	High-Resolution Computed Tomography
HSCT	Haematopoietic Stem Cell Transplant
i.v.	intravenous
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important Protocol Deviation
IPF	Idiopathic Pulmonary Fibrosis
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
Lck	Lymphocyte-specific Tyrosine-protein Kinase
LDH	Lactate Dehydrogenase
LFT	Liver Function Test

LPI	Last Patient In
LPLT	Last Patient Last Treatment
LPLVPE	Last-Patient-Last-Visit-Primary-Endpoint
Lyn	Tyrosine-protein Kinase Lyn
MACE	Major Adverse Cardiovascular Events
MCTD	Mixed Connective Tissue Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model with Repeated Measurements
MRI	Magnetic Resonance Imaging
n.a.	Not Applicable
NOA	Not Analysed
NOP	No Peak Detectable
NOR	No Valid Result
NOS	No Sample
NSIP	Non-Specific Interstitial Pneumonia
OPU	Operative Unit
PAH	Pulmonary Arterial Hypertension
PBMC	Peripheral Blood Monocytic Cells
PD	Pharmacodynamic(s)
PDGFR	Platelet-Derived Growth Factor Receptor
PedsQL™	Pediatric Quality of Life Questionnaire™
per os	Oral
PF-ILD	Progressive Fibrosing Interstitial Lung Disease
P-gp	Permeability Glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Set
PM	Polymyositis
PopPK	Population Pharmacokinetics
PT	Prothrombin Time
PTM	Planned Time
Q	Quaque, i.e. every
RA	Regulatory Authority

RA-ILD	Rheumatoid Arthritis associated ILD
RBC	Red Blood Count
REP	Residual Effect Period
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFTPC	Surfactant Protein Deficiency
SI	International System of units
SMC	Safety Monitoring Committee
SMQ	Standard MedDRA Query
6MWT	Six-Minute Walk Test
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus 2
SOC	Standard of Care
SOP	Standard Operating Procedure
SpO_2	Oxygen Saturation
Src	Proto-oncogene Tyrosine-protein Kinase
SSc-ILD	Systemic Sclerosis associated ILD
SUSARs	Suspected Unexpected Serious Adverse Reactions
$t_{1/2,ss}$	Terminal Half-life of the Analyte in Plasma at Steady State
$t_{max,ss}$	Time from Dosing to Maximum Measured Concentration of the Analyte in Plasma at Steady State
TKI	Tyrosine Kinase Inhibitor
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UIP	Usual Interstitial Pneumonia
ULN	Upper Level of Normal
US	United States
VEGFR	Vascular Endothelial Growth Factor receptor
w	Week(s)
[redacted]	
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

Vz/F_{ss}	Apparent Volume of Distribution during the Terminal Phase λz at Steady State following extravascular administration

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Childhood interstitial lung disease (chILD) comprises a complex and heterogeneous spectrum of rare respiratory disorders affecting infants and children [P19-02553] associated with varying prognosis. There is scant data in the literature on the epidemiology of paediatric ILDs. Overall, the prevalence of paediatric ILD is considered to be substantially lower than in adults [R11-5060, R12-0299, R12-0358, R12-0974, R14-4379, R17-2810, R17-2902, R17-2907, R03-2090, R03-2075, P16-01479], ranging from 1.5 to 3.8 per million [R12-2794, R16-4790, R17-2776] and incidence rates ranging from 1.32 to 162 per million person-years for children [R16-1141, R12-0299, R18-1147].

Similar to adults with ILD, some of whom can develop a progressive phenotype characterized by worsening symptoms, lung function decline and increased morbidity [P17-10582], some patients with chILD develop chronic lung fibrosis that is associated with significant morbidity and mortality. Although some ILDs (e.g. rheumatoid arthritis [RA]-ILD) can occur in both children and adults, certain ILDs occur more frequently in children (e.g. surfactant protein deficiency) [R16-4788] while others are almost exclusively found in adults (e.g. 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. Potential paediatric conditions likely to be associated with fibrosing ILD include, but are not limited to, the following:

- surfactant protein deficiency (SFTPC and ATP binding cassette subfamily A member 3 [ABCA3] mutations);
- chronic hypersensitivity pneumonitis (cHP);
- toxic/radiation/drug induced pneumonitis;
- post hematopoietic stem cell transplant (HSCT) fibrosis;
- connective tissue disease related disorders (e.g. juvenile rheumatoid arthritis [RA]/ juvenile idiopathic arthritis; Systemic Sclerosis [SSc], dermatomyositis/polymyositis [DM/PM]; mixed connective tissue disease [MCTD]) and sarcoidosis.

There are currently no approved therapies for the treatment of fibrosing interstitial lung disease associated with any of these conditions in children.

1.2 DRUG PROFILE

Mode of action
Nintedanib is a tyrosine kinase inhibitor (TKI) targeting fibroblast growth factor receptor (FGFR) 1–3, platelet-derived growth factor receptor (PDGFR) α and β, and vascular endothelial growth factor receptor (VEGFR 1–3) involved in fibrotic mechanisms active in patients with fibrosing interstitial lung diseases. In addition, nintedanib inhibits lymphocyte-specific tyrosine-protein kinase (Lck), tyrosine-protein kinase lyn (Lyn), proto-oncogene tyrosine-protein kinase (Src) [P08-08684] and colony-stimulating factor 1 receptor (CSF1R) kinases [P18-00197]. 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 inhibited migration, proliferation and transformation of human lung and skin fibroblasts from patients with IPF and SSc-ILD and the release of extracellular matrix protein [P14-07999, P14-17410, P15-06100, P14-02860, P16-05905, P17-06049, P18-05607]. In addition nintedanib attenuated cellular processes assumed to be involved in the initiation and progression of fibrosis, the release of pro-fibrotic mediators from peripheral blood monocytic cells (PBMC) [P17-06052] and the polarisation of macrophages to alternatively activated pro-fibrotic macrophages [P17-06049]. Nintedanib was effective in attenuating the progressive fibrotic lung pathology in animal models of lung fibrosis independent of the initial trigger, chemical, environmental, immunologic or transcriptional [P17-03310, P14-02860, P15-06100, P17-10564, P18-02512] suggesting a preclinical rationale to treat patients with lung fibrosis related to different underlying diseases.

Key pharmacokinetic characteristics

The pharmacokinetic characteristics of nintedanib have been evaluated in adults, for which a summary is provided in the following paragraph. For a more detailed description of the nintedanib profile in ILD please refer to the current Investigator's Brochure (IB) Nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis, Progressive Fibrosing Interstitial Lung Disease [c01783972-16].

A soft gelatin capsule formulation of nintedanib is used in humans. Maximum plasma concentrations (Cmax) occur between 2 to 4 hours after oral administration. Steady state is reached at the latest within one week of dosing. The absolute bioavailability of nintedanib is slightly below 5%. After food intake, a trend towards an increased systemic exposure (around 20%) and a delayed absorption is observed compared to administration under fasted conditions. Therefore nintedanib is recommended to be taken with food. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87; the terminal half-life is in the range of 7 to 19 h. Nintedanib is mainly eliminated via faeces (~93%), with minimal renal excretion (0.7%).

Drug interactions

Patients taking potent P-gp inhibitors (e.g. ketoconazole, erythromycin or cyclosporine) should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with nintedanib (see Section 4.1.2 and Table 4.1.2:2) [U10-1991, U13-1504, U13-1506, U13-1925, c02153150].

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Selection of an alternate concomitant medication with no or minimal P-gp induction potential should be considered [U13-1478-01, U13-1506, c02153150].

For specific restrictions of concomitant medication please refer to Section 4.2.2.1.

Residual Effect Period

The Residual Effect Period (REP) of nintedanib for the paediatric programme is 28 days.

Data from non-clinical studies
The antifibrotic effects of nintedanib have been demonstrated in various animal models of lung fibrosis, resembling features of idiopathic pulmonary fibrosis (IPF) [P17-03310, P18-05618], hypersensitivity pneumonitis (HP) [P18-08230], silicosis [P17-03310], systemic sclerosis associated ILD (SSc-ILD) [P17-10564] and rheumatoid arthritis associated ILD (RA-ILD) [P18-02512].

Data from clinical studies
Based on the demonstrated pre-clinical effects noted above, the potential benefits of nintedanib have been investigated in adults with idiopathic pulmonary fibrosis [P14-07514], SSc-ILD [P17-07763, P19-04387], and progressive fibrosing interstitial lung disease (PF-ILD) [P17-10582, P19-08802].

Results from the IPF and SSc-ILD programme in adults show nintedanib to be associated with statistically significant and clinically meaningful slowing of the progressive decline in lung function as measured by FVC over 1 year.

In the phase III study performed to investigate the efficacy and safety of nintedanib in subjects with non-IPF chronic fibrosing ILDs that were progressive despite management deemed appropriate in clinical practice (Trial 1199.247, INBUILD®) [P17-10582], nintedanib significantly reduced the progression of fibrosing ILD, as measured by the annual rate of decline in forced vital capacity (FVC) over 52 weeks compared with placebo in both in the overall population and in the co-primary population of subjects with a usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT. Compared with placebo, relative reductions of the annual rate of decline in FVC over 52 weeks of 57% in the overall population, 61% in patients with HRCT with UIP-like fibrotic pattern was observed. Consistent results were obtained in the complementary population of patients with HRCT with other fibrotic patterns [P19-08802]. Although the INBUILD® trial was not powered to study individual ILDs, subgroup analyses suggested that nintedanib had a consistent effect on FVC decline across diagnostic groups. The effect of nintedanib versus placebo on reducing the rate of FVC decline (mL/year) was consistent across subgroups by ILD diagnosis in the overall population [P20-02333].

The most commonly reported AEs were gastrointestinal disorders. Of those, the most frequent events were diarrhoea, nausea, and vomiting. Most of these events were of mild or moderate intensity, reported as non-serious, and were managed by symptomatic treatment and/or temporary interruption and/or reduction of the nintedanib dose. Diarrhoea, nausea, vomiting, which may lead to dehydration and/or electrolyte disturbances, and abdominal pain are considered adverse reactions of nintedanib treatment in adults. More patients in the nintedanib group than in the placebo group reported weight and appetite decrease as AEs. Weight decreased and appetite decrease are considered adverse drug reactions of nintedanib treatment.

Cases of drug-induced liver injury (DILI) have been observed with nintedanib treatment in adults. The majority of hepatic events occur within the first three months of treatment, therefore hepatic transaminase and bilirubin levels should be investigated upon the initiation

of treatment with nintedanib, at regular intervals during the first three months of treatment and periodically thereafter or as clinically indicated.

Considering that VEGFR inhibition might potentially be associated with an increased risk of bleeding, patients at known risk for bleeding or who required fibrinolysis, full-dose therapeutic anticoagulation, or high dose antiplatelet therapy have been excluded from participation in the nintedanib trials, and initiation of any of these therapies during the course of the trials required discontinuation of the study medication.

For a more detailed description of the nintedanib profile, please refer to the current IB Nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis and Progressive Fibrosing Interstitial Lung Disease [c01783972-16].

1.3 RATIONALE FOR PERFORMING THE TRIAL

This study is part of the Paediatric Investigation Plan (PIP) agreed with EMA for nintedanib in the treatment of chronic fibrosing ILDs with a progressive phenotype.

The study is conducted in patients 6 to 17 years old with clinically significant fibrosing ILD.

Based on the presumed similarities in underlying pathophysiology in fibrotic lung remodelling in adults and children and observed clinical efficacy in adults with fibrosing interstitial lung disease, e.g. systemic sclerosis associated ILD, idiopathic pulmonary fibrosis, and other progressive fibrosing ILDs, it is postulated that the anti-fibrotic effect of nintedanib may lead to similar benefit in a paediatric population with similar underlying pathophysiology.

As the conduct of a confirmatory efficacy study is deemed not feasible based on the low disease prevalence in children, a focused PK and safety evaluation of nintedanib in children and adolescents with clinically significant fibrosing interstitial lung disease is planned. Due to small patient numbers, a basket approach [P17-10582, R18-2970] will be used to group children and adolescents according to demonstrated evidence of lung fibrosis and clinical disease severity irrespective of clinical diagnosis to optimise feasibility. Supportive data on efficacy in the proposed paediatric programme will be collected to support inferences of clinical benefit and evaluation of the benefit-risk of nintedanib in the target population.

1.3.1 Similarities and differences in the condition between populations and pharmacological rationale

Fibroblast proliferation, migration and transformation have been shown to be fundamental processes in the common final path of fibrotic remodelling and several diseases resulting in lung fibrosis including IPF, chronic HP, SSc-ILD and RA-ILD [c01783972-16]. As such, the prevailing underlying hypothesis is that a similar final common pathway in fibrosing ILDs can be targeted with nintedanib and lead to clinical benefit (see pharmacologic rationale). Accordingly, clinical programmes with nintedanib have targeted patients with presumed similarities in pathophysiology based on demonstrated evidence of chronic fibrosing lung disease, irrespective of the underlying trigger [P17-07763; P17-10582].

While there is overlap between clinical diagnoses associated with lung fibrosis in paediatrics and adults, some diagnoses associated with lung fibrosis are specific to each population. The following paediatric conditions can be most frequently associated with lung fibrosis in paediatrics:

- surfactant protein deficiency (SFTPC and ABCA3 mutations [i.e. recessive disorder, suspected pathogenic variants or deletion/disruption]);
- chronic hypersensitivity pneumonitis (cHP);
- toxic/radiation and drug induced pneumonitis;
- post haematopoietic stem cell transplant (HSCT) fibrosis;
- connective tissue disease related disorders (e.g. juvenile rheumatoid arthritis [RA]/ juvenile idiopathic arthritis, SSc, dermatomyositis/polymyositis [DM/PM]; mixed connective tissue disease [MCTD])
- sarcoidosis.

In addition to difference in clinical diagnoses associated with fibrosing lung disease, the clinical course of fibrotic lung disease also differs between paediatrics and adults.

The data on the natural history of chronic fibrosing interstitial lung disease in children is limited. The available evidence suggests overall that the clinical course is associated with better outcome compared to adult ILDs with survival at 2, 4 and 5 years after symptom onset reported to be 83%, 72% and 64%, respectively [R09-5337]. This is compared to a median survival of 2.5–3.5 years from diagnosis in IPF [P11-07084], the most progressive form of fibrosing lung disease in adults. However, as previously mentioned there is a subgroup of children with fibrosing lung disease who experience significant morbidity and mortality [R09-5337].

Accelerated decline in lung function over time is one of the key clinical findings in adults with fibrotic ILDs and is considered one of the best predictors of disease progression and mortality [R10-6539, R06-4127, R10-2727, P12-09611, R14-1149, R12-3648, R14-1150, R06-4129, R17-1625, R18-3409, R18-3555]. Other independent predictors of mortality that have been identified in adults with fibrosing lung disease include older age, male gender, worse pulmonary function and radiological or histopathological extent of fibrosis, as well as presence of usual interstitial pneumonia (UIP) pattern on HRCT [P06-05020, R16-0754, R16-0756, R16-0758, R16-0752, R16-0755, R16-0560]. While there is limited data in paediatrics, a study assessed predictors of survival in a small cohort of children with various fibrosing ILDs and found a severity-of-illness score based on symptoms and oxygenation to be significantly associated with decreased survival [R09-5337]. There is limited data on serial lung function in children with fibrosing ILD available in the literature. Clinical parameters such as weight, crackles, digital clubbing, symptom duration or family history were not found to be associated with survival. As such, evaluation of clinically significant disease and evaluation of potential therapies in paediatric patients need to be tailored accordingly.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Based on a comprehensive clinical development programme in adult patients with 3 phase II and III studies in IPF (TOMORROW®, INPULSIS1® and INPULSIS2®), 1 phase III study in SSc-ILD (SENSCIS®) [P17-07763], and 1 phase III study in chronic fibrosing interstitial lung disease with progressive phenotype (INBUILD®) [P17-10582], nintedanib has been approved for the treatment of IPF in more than 70 countries and for the treatment of SSc-ILD in Europe, US, Japan, Australia, Canada, China and several other countries. In addition, nintedanib has been approved for the treatment of adults with chronic fibrosing interstitial lung diseases with a progressive phenotype in the US, Canada, Japan and has received a positive opinion in Europe. Nintedanib has shown a consistent benefit in slowing the rate of decline in lung function over 52 weeks across these indications [P14-07514, P19-04387, P19-08802].

Based on its mode of action and demonstrated effect in various pre-clinical models of ILD and demonstrated clinical benefit in various adult fibrosing ILDs (e.g. IPF, fibrosing ILDs with a progressive phenotype, and SSc-ILD), treatment of fibrosing ILDs with nintedanib in children and adolescents is expected to lead to similar clinical benefit as observed in adults.

1.4.2 Risks

Currently there is no experience with nintedanib in the paediatric population except for the current trial. However, the known risks of use in adults are expected in children and adolescents as well. The most frequently reported adverse reactions associated with the use of nintedanib in adults relate to the gastrointestinal system (i.e. diarrhoea, nausea, vomiting, abdominal pain), decreased appetite and hepatic enzyme increase. These events are mostly non-serious and are reversible with dose reductions or drug discontinuation. Less frequent and important adverse reactions include bleeding and drug induced liver injury (DILI) which may result in fatal outcome.

Additional risks specific for the paediatric population based on the mechanism of action of nintedanib have also been identified in preclinical animal studies, like a potential impact in maturation and growth, in bone development and in tooth development (see Table 1.4.2:1 for details).

The most frequently reported adverse reactions associated with the use of nintedanib in adults, and the potential risks specific to the paediatric population, will be carefully monitored.

Based on the pharmacological mechanism, existing non-clinical, clinical and post-marketing data, there is no indication that treatment with nintedanib may increase the risk for infection with SARS-CoV-2 or the risk for worsening the disease course of COVID-19. However, patients with chronic fibrosing interstitial lung diseases may be at risk of severe clinical courses due to the underlying disease, associated co-morbidities and potential use of immunosuppressive co-medications.

The trial related risk to the COVID-19 pandemic situation is the general risk of travelling to site and being at site for assessments. Risk mitigation measures and modifications to CTP standard procedures have been defined and are permitted to ensure IMP supply to patients and required safety monitoring while reducing the risk of exposure to SARS-CoV-2 related to center visits and planned examinations. See Section 6.1 and Appendix 10.9 for details.

Table 1.4.2:1 Overview of trial related risks

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product Nintedanib		
Adverse reactions reported in adults: • Gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting, abdominal pain)	Most frequent, mostly non-serious and reversible with dose reductions, temporary drug interruption or drug discontinuation.	Increased awareness of symptoms and early management, guideline to manage diarrhoea (Clinical Trial Protocol [CTP] Section 4.1.2), regular monitoring by SMC.
• Decreased appetite	Same as above.	Weight check every 12 weeks, regular monitoring by SMC.
• Hepatic enzyme increased	Same as above.	Increased awareness of symptoms and early management, guideline to liver enzyme elevations (CTP Section 4.1.2), regular monitoring by SMC, kits provided to conduct blood sampling at local laboratory/doctor/health care provider for intermediate liver function tests (LFTs) by central laboratory as needed (“a” visits).

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
• Drug-induced liver injury (DILI)	Rare but severe event may result in fatal outcome, thus under constant surveillance by sponsors and regulators.	Increased awareness and expedite reporting (AESI). Careful monitoring of liver function. Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.
• Bleeding	Less frequent compared to gastrointestinal disorders, may result in fatal outcome.	Increased awareness and expedite reporting (AESI). Patients at known risk for bleeding or who required fibrinolysis, full-dose therapeutic anticoagulation, or high dose antiplatelet therapy are excluded from participation in the trial.
• Foetal harm	Pre-clinical studies in animals have shown reproductive toxicity of this drug. [U07-1710, U07-1814].	Pregnancy testing conducted in all female patients at each visit on blood until end of treatment, and between visits on urines from Visit 4 until end of trial and at the Follow-up Visit (if acceptable), to ensure testing every 4-6 weeks. Females of childbearing potential are included only if sexual abstinence is standard practice, or if using a highly effective method of birth control in combination with a barrier method of birth control.

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Potential risks in adults relevant to the paediatric population • Gastrointestinal perforation	Based on mechanism of action and post-marketing data.	Increased awareness and expedite reporting (AESI).
Potential risks specific to the paediatric population, risk based on the nintedanib mechanism of action: • Impact in maturation and growth	VEGFR blockade results in decreased angiogenesis, which is essential for growth and development processes.	Monitor potential effects on growth by: Height (standing and sitting) and leg length measurement every 12 weeks. Regular evaluation by SMC.
• Impact in bone development and growth	In animal models, nintedanib has been shown to alter the epiphyseal growth plates of large bones (femur and tibia). These changes were reported during bone growth, and were reversible after discontinuation.	Monitor potential reversible effects on bone development and growth by: Regular evaluation by radiology expert, with skeletal growth monitoring (MRIs or x-rays of epiphyseal growth plates) at baseline and follow-up in patients with open physes at 12, 24, 36, 52 weeks and every 24 weeks thereafter until end of the study or closure of the physes. Expedited reporting of pathological findings identified on bone imaging (AESI). Regular evaluation by SMC.
• Impact on dentition	In animal models, nintedanib has been shown to impact tooth development. Tooth changes were major with altered tooth structure and	Monitor potential severe/irreversible effects on dentition by: Regular evaluation by dentist, with dental examination at baseline and

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	function which were irreversible. Changes occurred only during the growth phase of the teeth.	follow-up at 12, 24, 36, 52 weeks and every 24 weeks thereafter until end of the study. Expedited reporting of stunted growth identified on dental imaging (AESI). Regular evaluation by paediatric dentistry expert, with panoramic x-ray at baseline and follow-up at 24, 52 and every 48 weeks thereafter until end of the study. Regular evaluation by SMC.
Trial procedures		
• Radiation exposure	Required to monitor potential risk associated with study drug and confirm patient eligibility.	State of the art radiologic methods required, x-rays of epiphyseal growth plates only if MRI not possible in individual patients. Regular dental examination and panoramic x-ray at minimum time interval required to ensure safety. HRCT at baseline required only if acceptable HRCT not available within 12 months of Visit 1. [redacted] MRI/x-ray at EoT required only if previous MRI/x-ray not available within 12 weeks in the first year, 24 weeks thereafter. Panoramic x-ray at EoT required only if previous panoramic x-ray not available within 24 weeks.

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Other risks		
• Placebo treatment	Allow for blinded evaluation of safety over first 24 weeks of study (Part A)	Patients will be allowed to use SOC as determined by treating physician.
• Risk of contracting a SARS-CoV-2 infection		The number of site visits is limited to the minimum required for the successful conduct of the trial. Several measures are proposed for local implementation - if possible and needed - to ensure continued patient treatment, monitoring, and safety even if site visits are not possible (see Section 4.1.4, Section 6.1 and Appendix 10.9 for details).

An external Safety Monitoring Committee (SMC) will ensure monitoring of safety throughout the conduct of the study. The SMC will review individual and aggregated PK and safety data at regular intervals, advise the study team about the appropriateness of further enrolment and continuation/modification/premature interruption of the study, and might recommend dose modification and/or additional assessments (e.g. intermediate checks in those patients who switched from placebo to nintedanib at the end of the initial 24 weeks of treatment).

Investigational Medicinal Product (IMP) withdrawal criteria throughout the treatment phase of the study as defined by protocol should be adhered to (see Section 3.3.4.1).

Patients with co-morbidities associated with potentially increased risk to nintedanib will be excluded (see Section 3.3.3).

1.4.3 Discussion

Given the high unmet need for treatment options in paediatric fibrosing ILDs, the established clinical benefit and known safety profile of nintedanib in adults as well as the expected benefit of nintedanib in the paediatric fibrosing ILD, the benefit-risk of nintedanib in the target population is considered acceptable. The planned trial procedures and the associated-risk are deemed acceptable as they allow for timely identification of potential risks, discontinuation of treatment and possible reversal of adverse drug reactions.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of the study is to evaluate dose-exposure and safety of nintedanib in children and adolescents with fibrosing ILD.

2.1.2 Primary endpoints

Primary endpoints:

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

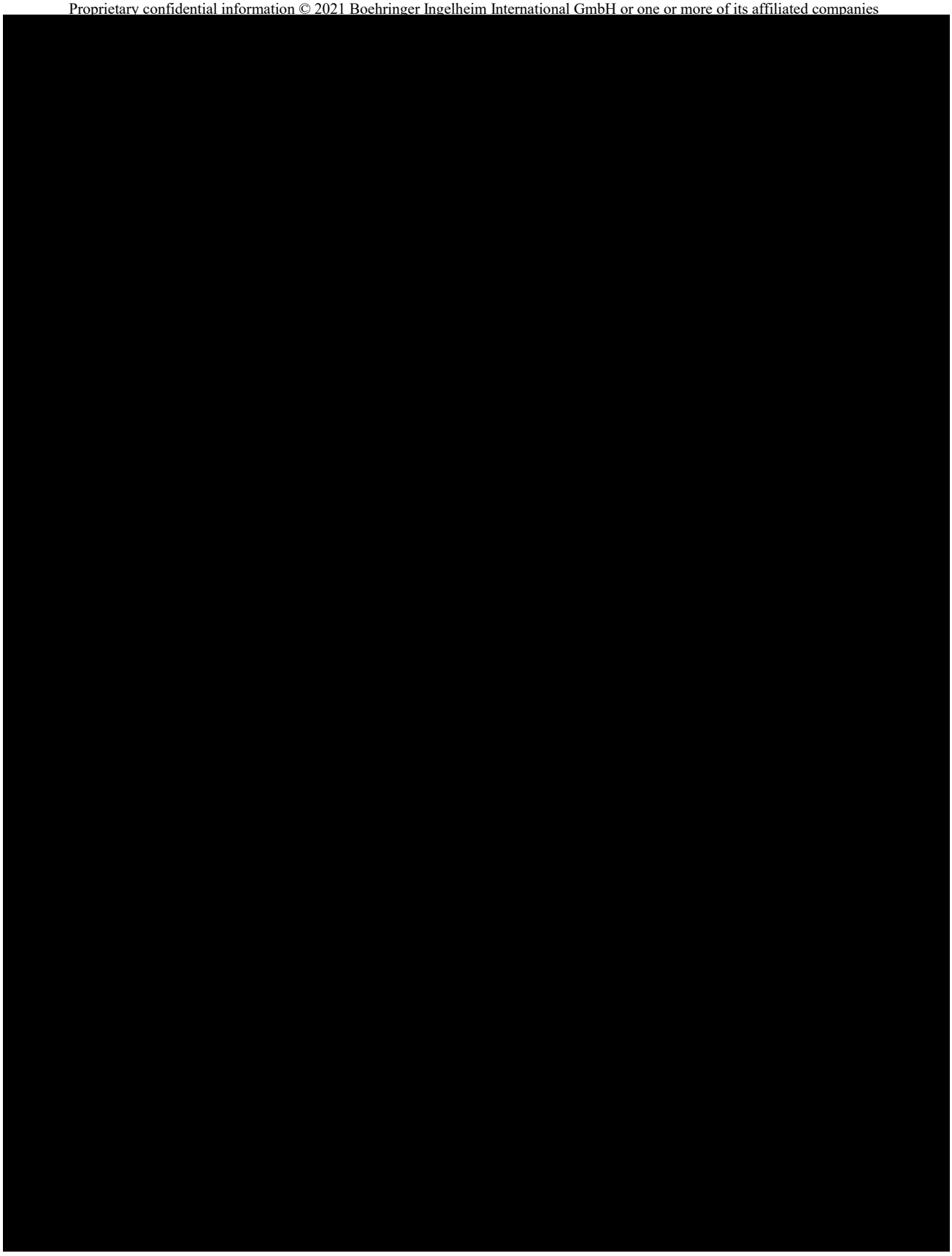
2.1.3 Secondary endpoints

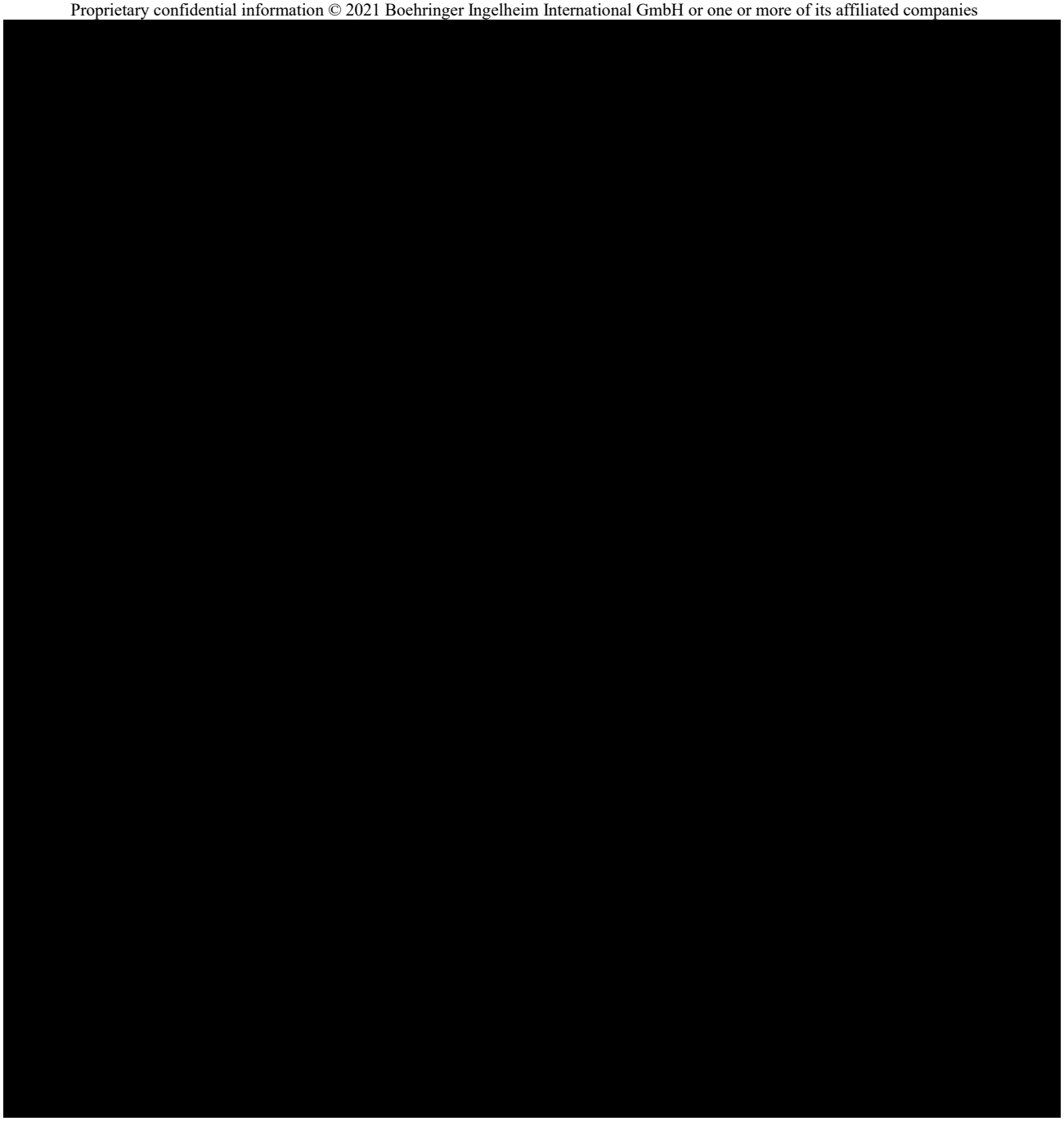
Secondary endpoints:

- N (%) of patients with treatment-emergent pathological findings of epiphyseal growth plate on imaging at week 24, and week 52*;
- N (%) of patients with treatment-emergent pathological findings on dental examination or imaging at week 24, and week 52*;
- N (%) of patients with treatment-emergent adverse events over the whole trial;
- Change in height, sitting height, leg length from baseline at week 24, week 52*, week 76*, and week 100*.
- Change in Forced Vital Capacity (FVC) % predicted from baseline at week 24, and week 52*;
- Absolute change from baseline in Pediatric Quality of Life Questionnaire™ (PedsQL™) at week 24, and week 52*;
- Change in oxygen saturation (SpO_2) on room air at rest from baseline at week 24, and week 52*;
- Change in 6-min walk distance from baseline at week 24, and week 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 hospitalization over the whole trial;
- Time to first acute Interstitial Lung Disease (ILD) exacerbation or death over the whole trial;
- Time to death over the whole trial.

*52 weeks, 76 weeks, 100 weeks time point will not be available for all patients.

[redacted]





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national, prospective, double blind, randomised, placebo-controlled clinical 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 years old) with clinically significant fibrosing interstitial lung disease.

All patients recruited for the study will enter a 4-week screening period (Visit 1 to Visit 2) (see Flow Chart and footnotes for permitted time window). At Visit 2 patients meeting in-/exclusion criteria will be randomised and enter the treatment period of the study. This period will consist of two parts: Part A and Part B (Figure 3.1: 1).

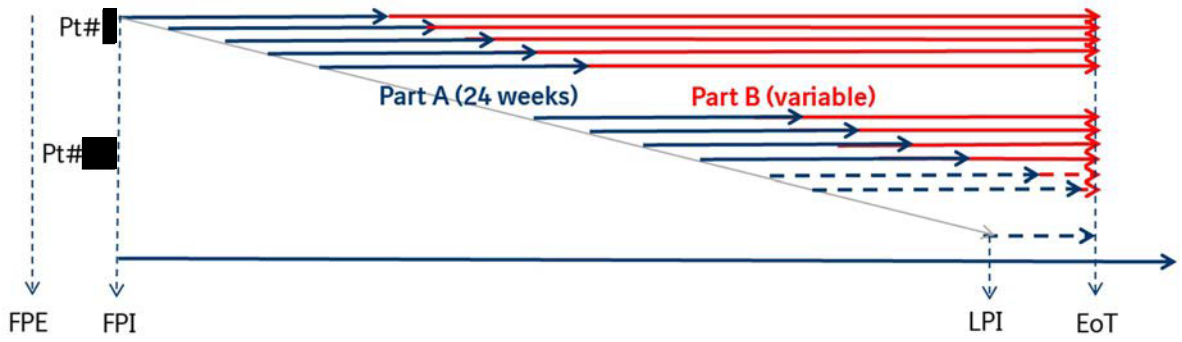


Figure 3.1: 1 Trial design

FPE: First Patient Enrolled; FPI: First Patient In (i.e. randomized); LPI: Last Patient In; EoT: End of Treatment.

During Part A patients will receive blinded randomised treatment (nintedanib or placebo 2:1) for 24 weeks. Following completion of Part A (Visit 6), patients will be switched to open label nintedanib (Part B) and will remain on treatment until the end of the study, or premature discontinuation. The duration of treatment in Part B is "variable" from patient to patient, depending on when the patient has entered the treatment period of the study. For the definition of "the end of the study" see Section 8.6.

The study will include two database locks (DBL 1 and DBL 2). The first DBL will be announced once 30 patients (at least 20 adolescents aged 12-17 years, and if feasible at least 10 children aged 6-11 years) have completed PK sampling at 26 weeks, or prematurely discontinued the trial (last-patient-last-visit-primary-endpoint). At this timepoint patient recruitment will close. Based on the data from DBL 1 (or updated DBL 1 data once the number of patients with sufficient PK data has been reached), the primary analysis and a benefit-risk assessment will be done and the clinical trial report for the primary analysis will be written. The timing of final DBL (DBL 2) and EoT visit will be communicated after confirming adequacy of PK data from DBL 1 (or updated DBL 1 data).

If no additional PK data are needed, all patients, including those who may have entered the study after targeted number (30 patients) have been randomised, will be scheduled for an EoT visit.

After the EoT visit, patients will enter a 4-week follow-up period (see Flow Chart and footnotes for permitted time window), unless they subsequently roll-over into the open label extension trial. The open label extension trial (1199-0378) will be initiated if supported by the benefit-risk assessment from DBL 1.

In the rare case that additional PK data is deemed necessary to complete the primary PK assessment, data from DBL 1 will be updated and the administrative DBL 2 will be postponed. Additional PK will be collected by switching ongoing study participants in Part A to Part B and/or recruiting new patients directly to Part B following screening if supported by the benefit-risk assessment. This decision will be made after discussion with the Safety Monitoring Committee (SMC) and properly documented. Once the decision is taken, all patients who did not yet complete Visit 6 (and were not prematurely discontinued) will be scheduled for Visit 6, complete all visit procedures (see Section 6.2.2 for details) and enter Part B. After two weeks of open label treatment each patient will attend Visit 7, and blood samples for PK analyses will be collected per standard procedures (see Flow Chart for PK blood sampling for details). If the number of patients in Part A is not sufficient, further patients will be screened and entered to Part B at the end of the screening period, if meeting eligibility criteria (see Section 3.3.2 and Section 3.3.3 for details).

Patients who prematurely discontinued trial medication will be asked to remain in the study and return to all regularly scheduled visits until the end of the trial. For details about procedures to be conducted at these visits please refer to Section 6.2.3. For those patients who are unable to complete the scheduled visits, every attempt will be made to get information on vital status at 24 weeks after randomization (i.e. the time of the data cut-off for the primary analysis), at 52 weeks and at the end of the trial. These requests will be outlined in the parental-information form and discussed during administration of the informed consent (the same applies to the assent form, where applicable).

For each patient, the study period is from the signature of the informed consent by the parent(s)/legal guardian until the patient's last visit of the study. Adverse events will be collected during the entire study period and considered treatment-emergent from first study drug intake until 28 days after drug discontinuation.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

Placebo design and treatment allocation

A placebo-controlled design is considered necessary for evaluating and interpreting the AE reporting.

While the safety profile is presumed to be similar to that observed in the adult studies including IPF, SSc-ILD and fibrosing ILDs with progressive phenotype, the availability of a

placebo arm will assist in the interpretation of any potential unexpected findings in this paediatric population.

In addition, though limited, use of a placebo group may allow for exploratory evaluation of the natural course of lung function and assess comparability of the study population to historical controls if available by then.

To minimise the potential negative impact of a placebo-control design on recruitment and taking into account the disease severity, use of standard of care as deemed clinically indicated by the treating physician will be allowed. In addition, as there are limited treatment options for the target population, after 24 weeks of double blind, placebo-controlled treatment all patients will be switched to open label nintedanib treatment.

Consistent with the primary objective of evaluating the safety of nintedanib in the target population, a 2:1 allocation is planned to minimize exposure to placebo and allow for more robust safety evaluation of active treatment.

Treatment duration

The planned duration of the placebo-controlled treatment is considered sufficient to evaluate the primary endpoint of PK as well as assess the incidence of the most frequent drug related AEs associated with nintedanib in the adult population, and potential AEs related to use of nintedanib in the paediatric population.

The most frequent AEs associated with nintedanib treatment in adults (e.g. increases in liver transaminase levels and/or bilirubin, diarrhoea, nausea, vomiting) can be adequately assessed with a treatment duration of 3 months. Since a comparable safety profile is expected in children and adolescents, a study duration of 6 months is considered acceptable. While there is no previous clinical experience of nintedanib in the paediatric population, review of the literature of the effect of VEGF inhibition in children suggest that 6-month observation is adequate to evaluate potential acute effects on growth [R18-1476, R18-1477].

Moreover, the overall exposure to active treatment based on the proposed study design allows for collection of long term safety monitoring data of potential paediatric specific AEs (i.e. bone and teeth effects), which may take longer to develop. Based on to the current design, assuming a recruitment time of 18 months, the treatment period for the minimum targeted 30 subjects is expected to be minimum 26 weeks, with an average nintedanib exposure of approximately 12 months, and >2-year exposure in early enrolled patients. As such, data collected beyond 6 months will provide longer term safety and efficacy information.

Sample Size

The target sample size of a minimum of 30 patients is based on the sample size estimation for the primary evaluation of PK and feasibility. Although the planned basket approach makes it feasible to evaluate this extremely rare patient population, one of the limitations of this approach is the heterogeneity of the study populations, especially in evaluating efficacy outcomes of potential interest (e.g. lung function). Given the high unmet medical need, lack of therapeutic option and the potential for more robust assessment of efficacy, study enrolment into the treatment phase will remain open until 30 patients (at least 20 adolescents

aged 12-17 years, and if feasible at least 10 children aged 6-11 years) have completed PK sampling at 26 weeks, or prematurely discontinued the trial. This approach will allow for any eligible patients identified beyond the minimum targeted 30 subjects to have access to study drug. All PK and clinical data available at DBL 1 (or updated DBL 1) will be used in the primary analysis to allow for more robust estimates of exposure and potential treatment effect.

3.3 SELECTION OF TRIAL POPULATION

At least 30 paediatric patients (male and female 6 years old and older, including at least 20 adolescents aged 12-17 years) with documented clinically significant fibrosing interstitial lung disease will be randomised.

Patients under the age of 6 years will be excluded from the current study. This is based on the potential higher risk of nintedanib administration in children younger than 6 years, limited evidence to support the scientific rationale of potential benefit of nintedanib, and challenges in evaluating potential clinical benefit as established in adults, in this paediatric subset.

A log of all patients enrolled into the trial (i.e. who have an informed consent signed by the parent(s)/legal guardian) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether patients have been treated with investigational drug or not.

Re-enrolment of screen failed patients will be permitted. Patients who did not qualify for randomisation during the early months of the recruitment period might qualify for randomisation during the late months of the recruitment period of the study. A previous 'screening failure' patient will sign a new informed consent and get a new unique patient number. The previous patient number will be collected via the electronic Case Report Form (eCRF).

If a patient is enrolled by error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

Patient recruitment is expected to be conducted in approximately 24 countries and approximately 70 sites. Each site is expected to enrol 1-2 patients, some sites might not be able to randomize any patients.

3.3.1 Main diagnosis for trial entry

The study will be conducted in paediatric patients with clinically significant fibrosing interstitial lung diseases as defined in protocol (refer to Section 3.3.2 and Section 3.3.3). Given the low prevalence of individual (and even grouped) diagnoses, a basket approach grouping patients based on similarity in underlying pathophysiology in fibrotic remodelling is considered required for the feasibility of the current study.

Potential diagnoses likely to be associated with a chronic fibrosing lung pathology include, but are not limited to:

- Surfactant protein deficiency (SFTPC, ABCA3 mutations [i.e. recessive disorder, suspected pathogenic variants or deletion/disruption]);
- chronic hypersensitivity pneumonitis (cHP);
- Toxic/radiation/ and drug induced pneumonitis;
- Post Haematopoietic Stem Cell Transplant (HSCT) fibrosis;
- Connective tissue disease related disorders (e.g. juvenile rheumatoid arthritis [RA]/ juvenile idiopathic arthritis, SSc, dermatomyositis/polymyositis [DM/PM], mixed connective tissue disease [MCTD])
- Sarcoidosis

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Children and adolescents 6 to 17 years old at Visit 2.
2. Signed and dated written informed consent and assent, where applicable, in accordance with ICH-GCP and local legislation prior to admission to the trial.
3. Male or female patients. Female of childbearing potential (WOCBP)[1] must confirm that sexual abstinence is standard practice and will be continued until 3 months after last drug intake, or be ready and able to use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly, in combination with one barrier method, from 28 days prior to initiation of study treatment, during treatment and until 3 months after last drug intake. Sexual abstinence is defined as abstinence from any sexual act that may result in pregnancy. A list of contraception methods meeting these criteria is provided in the parental information and in Section 4.2.2.3.
4. Patients with evidence of fibrosing ILD on HRCT within 12 months of Visit 1 as assessed by the investigator and confirmed by central review. [See Section 3.3.2.1 for details.]
5. Patients with FVC % predicted ≥25% at Visit 2.

   [Note: Predicted normal values will be calculated according to GLI (Global Lung Initiative), see Section 5.1.1 for details.]
6. Patients with clinically significant disease at Visit 2, as assessed by the investigator based on any of the following:
   - 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

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- other measures of clinical worsening attributed to progressive lung disease (e.g. increased oxygen requirement, decreased diffusion capacity).

Instructions on Fan score are given in Appendix 10.1.

3.3.2.1 Evidence of fibrosing ILD

Determination of fibrosing ILD on HRCT by the investigator will be 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 will be based on pre-defined imaging criteria to ensure consistency. The imaging criteria to be used will be determined by expert consensus and included in the imaging manual provided to study sites.

For patients with previous pathological findings of fibrosis on lung biopsy, confirmation of fibrosis on HRCT will be made if at least one of the following imaging criteria are met within 12 months of screening visit (Visit 1) as confirmed by central review:

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

Co-existing features cystic abnormalities or ground glass opacity are acceptable. Co-existing multifocal non-fibrotic, non-dependent consolidations (e.g. organizing pneumonia, infection) will not be allowed.

Any of the following biopsy findings or diagnoses will be 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
- Evidence of lobular remodelling on a significant* component of the lung biopsy
- Honeycomb lung

*based on the opinion of the central reviewer.

For patients without any documented lung biopsy or whose biopsy results do not meet the biopsy criteria for fibrosis listed above, at least two of the following imaging findings are required on at least two HRCT scan (most recent one must be within 12 months of Visit 1): reticular abnormality, traction bronchiectasis, architectural distortion with/without ground glass opacification, honeycombing, cystic abnormality.

3.3.3 Exclusion criteria

1. AST and/or ALT >1.5 x ULN at Visit 1.
2. Bilirubin >1.5 x ULN at Visit 1.
3. Creatinine clearance <30 mL/min calculated by Schwartz formula at Visit 1.

   [Note: Laboratory parameters from Visit 1 have to satisfy the laboratory threshold values as shown above. Visit 2 laboratory results will be available only after

randomization. In case at Visit 2 the results do no longer satisfy the entry criteria, the Investigator has to decide whether it is justified that the patient remains on study drug. The justification for decision needs to be documented. Laboratory parameters that are found to be abnormal at Visit 1 are allowed to be re-tested (once) if it is thought to be a measurement error (i.e. there was no abnormal result of this test in the recent history of the patient and there is no related clinical sign) or the result of a temporary and reversible medical condition, once that condition is resolved.]

4. Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment) at Visit 1.
5. Previous treatment with nintedanib.
6. Other investigational therapy received within 1 month or 5 half-lives (whichever is shorter but ≥1 week) prior to Visit 2.
7. Significant pulmonary arterial hypertension (PAH) defined by any of the following:
    a. Previous clinical or echocardiographic evidence of significant right heart failure
    b. History of right heart catheterization showing a cardiac index ≤2 l/min/m²
    c. PAH requiring parenteral therapy with epoprostenol/treprostinil
8. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
9. Cardiovascular diseases, any of the following:
    a. Severe hypertension, uncontrolled under treatment, within 6 months of Visit 1. Uncontrolled hypertension is defined as
        i. In children 6 to ≤12 years old: ≥95th percentile + 12 mm Hg or ≥140/90 mm Hg (whichever is lower) (systolic or diastolic blood pressure equal to or greater than the calculated target value)
        ii. In adolescents 13 to 17 years old: systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg
    b. Myocardial infarction within 6 months of Visit 1
    c. Unstable cardiac angina within 6 months of Visit 1
10. Bleeding risk, any of the following:
    a. Known genetic predisposition to bleeding
    b. Patients who require
        i. Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)
        ii. 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. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) are not prohibited.]
    c. History of haemorrhagic central nervous system (CNS) event within 12 months of Visit 1
    d. Any of the following within 3 months of Visit 1:
        i. Haemoptysis or haematuria
        ii. Active gastro-intestinal (GI) bleeding or GI – ulcers
        iii. Major injury or surgery (investigator's judgment)
    e. Any of the following coagulation parameters at Visit 1:

i. International normalized ratio (INR) >2
ii. Prolongation of prothrombin time (PT) by >1.5 x ULN
iii. Prolongation of activated partial thromboplastin time (aPTT) by >1.5 x ULN

11. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1.
12. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin).
13. Patients with documented allergy to peanut or soya.
14. Other disease that may interfere with testing procedures or in the judgment of the investigator may interfere with trial participation or may put the patient at risk when participating in this trial.
15. Life expectancy for any concomitant disease other than ILD <2.5 years (investigator assessment).
16. Female patients who are pregnant, nursing, or who plan to become pregnant while in the trial.
17. Patients not able or willing to adhere to trial procedures, including intake of study medication.
18. 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 considered by the investigator to be due to glucocorticoid therapy may be included.
19. Patients <13.5 kg of weight at Visit 1 (same threshold to be used for male and female patients).

Instructions about how to assess creatinine clearance are given in Appendix 10.2.
Recommendations for blood pressure measurements in children and adolescents are given in Appendix 10.4.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or have withdrawn consent (and/or withdrawn assent, where applicable) to trial participation as a whole ("withdrawal of consent") with very different implications; please see Section 3.3.4.1 and Section 3.3.4.2 below.
Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and eCRF. If applicable, consider the requirements for Adverse Event collection and reporting (please see Section 5.2.7.2.1 and Section 5.2.7.2.2).

All data collected will be reported, including data of patients who discontinue/withdraw from treatment or assessments after randomization/entering the active treatment phase of the study.
If consent/assent to trial participation is withdrawn, data collection will stop at time of consent/assent withdrawal.

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, and or the parent(s)/legal guardian wants the patient to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.

In the following cases discontinuation of trial medication is highly recommended. Only in special circumstances the investigator, upon thorough assessment of all available clinical data and taking into consideration the potential risks associated with administration of nintedanib, may decide not to withdraw the trial medication, even though one or more of the below mentioned criteria are fulfilled. In such a case, continuation of treatment with trial medication should be discussed with the patient's parent(s)/legal guardian, and the decision and reasoning documented in the source data.

- Major surgery, including any abdominal or intestinal surgery.
- Anti-coagulation. Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, heparin, hirudin, direct thrombin inhibitors, etc.), or high-dose antiplatelet therapy. Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) is allowed.
- Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction.
- Increased risk of bleeding e.g. haemorrhagic CNS event, gross / frank haemoptysis or haematuria, active gastro-intestinal bleeding or GI-ulcers.

The trial medication has to be permanently discontinued in the following circumstances:

- The patient experiences signs of hepatic injury, as defined in Section 5.2.7.1.4.
- In the opinion of the Investigator, the patient experiences unacceptable adverse events despite dose adjustments and supportive care, as defined in Section 4.1.2.
- The patient needs to take concomitant medication that is restricted as defined in Section 4.2.2.
- The patient can no longer receive trial treatment for medical reasons (such as adverse events, other diseases, or pregnancy).
  If a patient becomes pregnant during the trial the investigational product must be discontinued immediately, and the patient will be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the clinical trial report (CTR) until patient´s last visit, and any events thereafter will be reported in the Boehringer Ingelheim (BI) drug safety database. Refer to Section 5.2.7.2.3 for detailed information on event reporting in case of pregnancy.

In case of discontinuation of trial medication, it is of utmost importance for the robustness and integrity of the trial results that the patient remains in the study and returns to all

regularly scheduled visits until the end of the trial. For those patients who are unable to complete the scheduled visits, every attempt will be made to get information on vital status at 24 weeks after randomization, i.e. the time of the data cut-off for the primary analysis, at 52 weeks after randomization and at the end of the trial, as outlined in the Flow Chart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patient's parent(s)/legal guardian may withdraw their consent to trial participation (and/or the patient may withdraw assent, where applicable) at any time without the need to justify the decision.
If a patient's parent(s)/legal guardian wants to withdraw consent (and/or the patient wants to withdraw assent, where applicable), the investigator should be involved in the discussion with the parent(s)/legal guardian (and/or the patient) and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational medicinal products are nintedanib soft capsules 150 mg, 100 mg, 25 mg, and matching placebo capsules.

Nintedanib soft capsules 100 mg (oblong shape, 6.2 mm diameter and 16.3 mm length) and 150 mg (oblong shape, 7.1 mm diameter and 17.6 mm length) are commercially available for adults. Nintedanib soft capsules 25 mg of smaller size (oval shape, 5.1 mm diameter and 8.0 mm length) have been developed for this trial in the paediatric population. The 75 mg and 50 mg doses will be provided as multiples of the newly developed 25 mg dosage strength.

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

- 4 x 25 mg for the 100 mg
- 6 x 25 mg for the 150 mg

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Test product 1

Substance:	Nintedanib (Ofev®)
Pharmaceutical formulation:	Soft gelatin capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	150 mg, 100 mg, 25 mg
Posology:	150 mg, or 100 mg, or 3x25 mg, or 2x25 mg, or 25 mg, each b.i.d.
Mode of administration:	Oral (swallowed)

Table 4.1.1:2 Test product 2

Substance:	Placebo
Pharmaceutical formulation:	Soft gelatin capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Placebo to 150 mg, 100 mg, 25 mg
Posology:	Placebo to 150 mg, or 100 mg, or 3x25 mg, or 2x25 mg, or 25 mg, each b.i.d.
Mode of administration:	Oral (swallowed)

4.1.2 Selection of doses in the trial and dose modifications

In order to match the systemic exposure reached in adult IPF patients, the nintedanib doses in paediatric patients were predicted based on body weight dependent allometric scaling (scaling of adult clearance using an exponent of 0.75, consistent with the exponent estimated in population pharmacokinetics [PopPK] analyses in adults; refer to the current version of the Investigator's Brochure Nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis and Progressive Fibrosing Interstitial Lung Disease [c01783972-16] for details). This approach is considered acceptable, assuming a minor role of developmental changes referring to nintedanib PK for the selected target population. A population mean nintedanib exposure of 80% to 125% compared to adult IPF patients treated with 150 mg b.i.d. was targeted for the determination of the planned doses by body weight bin in the paediatric population as provided in Table 4.1.2: 1.

The patient's weight will be measured at screening, at randomization and at each IMP dispensing visit thereafter (see Flow Chart for details). At randomization the dose assigned will be based on the patient's weight at baseline (Visit 2). At subsequent visits the dose will be adjusted for any changes of the patient's weight resulting in a change of the body weigh bin. IRT will assign the proper dose based on the patient's weight recorded at the respective visit.

Table 4.1.2: 1 Dose assignment and dose reduction possibilities based on body weight bins according to ICH E11

Body weight bin	**Weight range**	**Dose (b.i.d.)**	**Capsule strengths**	**Dose reduction possibility (b.i.d.)**	**Capsule strengths**
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)

* Patients <13.5 kg of weight are excluded from the trial

Based on population anthropometric measures of weight by age, most children younger than 10 are expected to fall into body weight bin 1–2, younger adolescents in bin 3 and older ones in bin 4.

Similar to the adult dosing schedule [P17-10582], treatment interruption and dose reduction are allowed as medically indicated.

Criteria for dose reduction / treatment interruption

Treatment should be interrupted in case the patient experiences a weight decrease below 13.5 kg. Treatment can be resumed when patient's weight reaches the threshold of 13.5 kg.

If a patient experiences a drug related adverse event, the dose can be reduced to the next lower dose and the dose can be re-started after recovery. The dose reduction scheme in Table 4.1.2: 1 should be considered to manage adverse events.

The dose can be reduced without prior interruption, i.e. immediately stepping down from one dose to the next dose.

If the reduced dose is well tolerated, re-escalation is 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. If this occurs between scheduled visits, this will also require an unscheduled visit.

Dose reduction and re-increase are allowed at multiple occasions.

No further dose reduction outside of those listed will be allowed. In case of persistent adverse events observed at the reduced dose, or severe effects at the starting dose, permanent treatment discontinuation should be considered.

Temporary treatment interruption is allowed to manage adverse events (see below for details).

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

The criteria to be followed for treatment interruption, re-start and re-escalation are shown in Table 4.1.2: 2.

Table 4.1.2: 2 Allowed treatment reduction / interruption periods:

	AEs considered related to study drug	**AEs or other events not considered related to study drug**
Maximum interruption	4 weeks	8 weeks
Recommended restart of treatment	with reduced dose per Table 4.1.2: 1	with the same dose as before interruption
Re-escalation	re-escalation to the dose assigned per Table 4.1.2: 1 may occur any time per investigator judgement	n.a.

To manage diarrhoea and liver enzyme elevations guidelines similar to the adult programme are provided in the paediatric programme.

- Management of diarrhoea

Diarrhoea is a known and the most frequent side effect of nintedanib treatment. However, potential causes for diarrhoea other than trial medication should always be considered and treated accordingly (e.g. viral infections, bacterial overgrowth, and antibiotic treatment). Diarrhoea should be managed as early as possible after onset of first symptoms with standard antidiarrheal symptomatic treatment, e.g. loperamide.
If diarrhoea persists despite optimal symptomatic treatment, treatment interruption and/or dose reduction of nintedanib should be considered. Table 4.1.2: 3 shows the recommendations for children and adolescents with the appropriate age and weight-adjusted dosing.

Table 4.1.2: 3 Management of diarrhoea (considered related to trial medication) in children and adolescents

Description	Symptomatic Treatment*	Action with trial medication
Diarrhoea with increase of <4 stools per day over baseline[1]	Initiate anti-diarrhoeal medicines at first signs of symptoms e.g. loperamide, as per the age-adjusted dosing regimen (Table 4.1.2:4) until bowel movements cease for 12 hours. Monitor for signs or symptoms of dehydration. Consider oral rehydration therapy.	Continue same trial medication dose.
Diarrhoea with increase of 4 to 6 stools per day over baseline[1]	Initiate/continue anti-diarrhoeal medicines; If diarrhoea of this severity persists for ≥48 to 72 hours assess for dehydration and electrolyte imbalance; In addition, consider i.v. fluids and electrolyte replacement as clinically indicated.	If diarrhoea persists for ≥48 to 72 hours despite optimal symptomatic care: 1. Interrupt trial medication until recovery. 2. Reduce dose to the next lower dose after recovery. 3. Re-escalate to the weight-adjusted dose within 4 weeks if deemed clinically appropriate.
Diarrhoea with increase of ≥7 stools per day over baseline[1]; stool incontinence, **or** **life threatening consequences**	Follow recommendations above. In addition, consider stool work-up to exclude infectious colitis; adequate i.v. fluid replacement ≥24 hours, hospitalization as clinically indicated; consider referral to a GI specialist to rule out potential differential diagnoses.	1. Interrupt trial medication until recovery. 2. Reduce dose to the next lower dose after recovery. 3. Consider re-escalation within 4 weeks to the weight-adjusted dose if deemed clinically appropriate. In case of reoccurrence of diarrhoea of this severity despite optimal symptomatic treatment and dose reduction, treatment with trial medication should be permanently discontinued.

Footnotes:

* Other potential causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, bacterial overgrowth, antibiotic treatment)

[1] Baseline defined as usual stools/day prior randomization.

Table 4.1.2: 4 Loperamide dose regimen based on group age

Group age	**Posology**
Children 6-8 years	One 5 ml (1 mg) dose three or four times daily with the duration limited to 3 days
Children 9-11 years	Two 5 ml (1 mg) doses four times daily with the duration limited to 5 days
Children 12-17 years	4 mg followed by 2 mg after each loose stool or every 2-4 hours to a maximum of 12 mg/day

- Management of liver enzyme elevations

Nintedanib can be associated with increased liver enzymes. Concomitant use of other drugs known to cause liver enzyme elevations should be evaluated. For a detailed guidance on how to manage liver enzyme elevations, please refer to Table 4.1.2: 5.

Table 4.1.2: 5 Recommendations for managing liver enzyme elevations

	AST or ALT increase to			Signs of hepatic injury*
	>1.5x to <3x ULN	≥3x to <5x ULN and no signs of hepatic injury	≥5x to <8x ULN and no signs of hepatic injury	
Visit 2 (randomization)	Permanently discontinue trial medication or justify continuation[1]	Permanently discontinue trial medication	Permanently discontinue trial medication	Permanently discontinue trial medication
Any other Visit	Continue as planned[2]	Reduce dose or interrupt trial medication[3]	Interrupt trial medication	Permanently discontinue trial medication
		Close observation[4] After 2 weeks or any time later	Close observation[4] After 2 weeks or any time later	**CLINICAL EVALUATION OF HEPATIC-INJURY**[5]
	<3x ULN	≥3x ULN	<3x ULN	≥3x ULN
	Reduced: return to initial dose. Interrupted: restart at reduced dose. Monitor every 2 weeks for at least 8 weeks	Permanently discontinue trial medication Close observation[4]	Restart at reduced dose Monitor weekly for 4 weeks, then every 2 weeks for at least 8 weeks	Permanently discontinue trial medication. Close observation[4]

Footnotes:

*Signs of hepatic injury are defined as

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥2 fold ULN
- ALT and/or AST ≥3 fold ULN and unexplained INR >1.5
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

[1]Investigator to confirm in writing that continuation is justified (e.g. intermittent fluctuation of transaminases).
[2]According to visit schedule. Consider additional control visits as adequate.
[3]To be decided by Investigator, based on individual risk assessment.
[4]Close observation: Re-test ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils within 48 to 72 hours, then approximately 7 days, then approximately 2 weeks by using intermediate visit lab kit.

Initial assessment of liver enzyme elevation should be performed at the investigational site. Blood samples for additional monitoring may be collected at the investigational site, primary care physician or external laboratory with specific trial lab kits and sent to the central laboratory for analysis.

- Management of acute ILD exacerbations

In case of acute ILD exacerbations or clinical deterioration, all treatment options considered adequate by the Investigator are allowed. The patient may interrupt study treatment for up to 8 weeks, if necessary (e.g. if short-term full anticoagulation is performed).

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 2:1 ratio (nintedanib:placebo) at Visit 2 (i.e. at start of Part A) via Interactive Response Technology (IRT) stratified by age group (6 - <12 years; 12 - <18 years). Access to the codes will be controlled and documented. A validated randomisation software will be used to generate the randomisation. Technical and statistical features of the process of treatment allocation are described in Section 7.4.

After completion of 24 weeks of blinded treatment, at Visit 6 (i.e. at start of Part B) each patient will be assigned via IRT to open label treatment with nintedanib, until EoT or premature discontinuation.

4.1.4 Drug assignment and administration of doses for each patient

For the individual patient the start of treatment period is planned on the day of randomization at Visit 2, and the end of treatment period is planned at the EoT visit; the last dose of trial medication should be taken in the evening before the EoT visit.

During the treatment period the treatment for an individual patient will be assigned by means of an IRT contact during scheduled clinic visits detailed in the Flow Chart.

The investigational product should only be dispensed to parents/caregiver(s) (or patients if applicable based on their maturity) if the patient was entered to the treatment phase of the study, during clinic visits as defined by protocol and by authorized personnel as documented in the “Trial Staff List”.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, please see Section 6.1), physical patient visits to the sites may not be feasible or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue trial treatment. Where permitted by local law and regulations, trial medication may be shipped directly to the patients’ home. If the defined minimum frequency of trial procedures cannot be adhered to, discontinuation from trial medication should be considered. See Appendix 10.9 for details.

Wallets each containing 84 capsules (25 mg), or 56 capsules (100 mg and 150 mg) will be dispensed to the patient, with sufficient coverage until the next dispensing visit. One reserve wallet will be dispensed at Visit 2 and at Visit 6 and replaced as needed (e.g. in case of dose change requiring unit strength change, or use-by-date before the date planned for the next clinic visit) thereafter. At Visit 6 any remaining wallet, including reserve, dispensed to the patient while the patient was taking part in the double-blind part of the study will be collected, and open label wallets will be dispensed.

Based on the assigned dose, including possible dose reduction, the daily dose of trial medication will consist of 1 capsule (150 mg, 100 mg, or 25 mg strength) or 2 capsules (25 mg strength), or 3 capsules (25 mg strength) to be taken per os twice daily (b.i.d.) (see Table 4.1.2: 1). Patients not able to swallow the 150 mg strength or the 100 mg strength capsule will have the possibility to take the 25 mg strength capsules (6 or 4 capsules per dose, respectively). To obtain kits with smaller capsules, an unscheduled visit should be registered in IRT. Once smaller capsules have been assigned, IRT will not allow to switch back to bigger capsules.

The patient should take the capsules twice daily, at about the same time every day (between 06:00 and 11:00 in the morning, 18:00 and 23:00 in the evening), with a dose interval of approximately 12 hours from one dose to the next dose.

The patient should swallow the whole capsules with water (a glass, approximately 250 mL) and should not chew or crush the capsules. If contact with the content of the capsule occurs, hands should be washed immediately and thoroughly. As nintedanib may cause stomach discomfort, the patient is recommended to take the capsules with food, i.e. during or immediately before or after a meal.

In case a dose is forgotten, the dose should be skipped if the time window to the next dose is less than 8 hours. The following dose should be taken according to the protocol. No catch up of missed doses is permitted.

In case of adverse events requiring a dose reduction between planned visits (see Section 4.1.2 for details), the patient will attend an unscheduled visit. The investigator will visit the patient, record the reason for dose change, assign the new dose and instruct the patient and parent(s)/legal guardian on the number of capsules to be taken in the morning and in the evening until the next visit. Drug accountability will be completed carefully. Please refer to Section 6.2.2 for instructions.

In case of adverse events requiring a dose interruption please refer to Section 4.1.2 for instructions.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The randomisation codes will be provided to bioanalytics for analysis purpose during conduct of the study to allow for the exclusion from the analyses of pharmacokinetic (PK) samples

taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until DBL 1.

At DBL 1 the trial will be unblinded by the sponsor.
In order to enable early analysis of PK, selected non-trial personnel from the sponsor involved in the PK analyses will be unblinded. The planned preliminary analyses will be conducted on a continuous basis and will focus purely on PK (no efficacy or safety outcomes will be analysed at that time). Available PK data will be provided to the SMC for consideration when evaluating the safety of the trial. Measures will be taken to ensure the integrity of the ongoing trial at the time of PK unblinding until the time of DBL 1. No individual unblinding information will be shared, however it could be communicated to the trial team how many patients with evaluable PK data are missing to reach the target. The process for unblinding as well as the trial team functions to be unblinded will be defined in the preliminary PK analysis logistics plan. In addition, a dedicated database snapshot (no partial DBL) will be generated after 'last-patient-last-visit-primary-endpoint' (LPLVPE) prior to DBL 1 to allow for development and refinement of exposure-response models ("Fast-track" PK/PD analysis) referring to FVC and the most relevant safety variables (e.g. diarrhoea and liver enzyme elevations). Only personnel involved in the exposure-response analyses will be granted access to the unblinded data before DBL 1, whereas the trial team and all other functions not involved in the exposure response analyses will remain blinded. The analysis plan for the exposure-response analysis as well as the Trial Statistical Analysis Plan (TSAP) will be finalized and signed prior to the database snapshot for 'fast-track PK/PD analyses'. No formal interim report will be generated.

The SMC will review unblinded data. The independent statistician of the SMC will receive the randomization code to allow the required analyses on unblinded data. The independent statistician will ensure that all unblinded information remains within the SMC.

Patients, investigators and any other site personnel will remain blinded with regard to the randomised treatment assignments until after the final database lock (DBL 2).

For rules of breaking the code for an individual or for all patients in emergency situations see Section 4.1.5.2.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. In case the automated unblinding option via the IRT system is malfunctioning, the IRT service provider can be contacted (24 hours a day coverage) and the treatment allocation can be obtained. IRT support has direct access to the database and the treatment information can be manually obtained in case the automated process is not working properly. Details about this process will be included in the ISF.

Emergency unblinding must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the high unmet medical need and lack of therapeutic options, a patient which is unblinded during Part A may be given the option to continue the trial and receive active treatment (nintedanib) until the end of the study, if there are no safety concerns and after approval by the sponsor.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated Contract Research Organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

The investigational medicinal product will be packaged in blister cards. Blisters cards will be packaged into one child-resistant tamper-evident wallet. Each wallet will be labelled with a multi-language booklet according to the requirements of the participating countries.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Trial Manager (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / Ethics Committee (EC),
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority (RA), e.g. competent authority (CA),
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- In countries where it is required, availability of the proof of a medical license for the Principal Investigator,
- In the US, availability of FDA Form 1572.

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed, nor any specific requirements for handling of trial medication in case of emergency (e.g. no specific antidote to be given, no other particular medical intervention required in connection with overdose).

Treatment interruption and dose reduction should be considered to manage adverse events, as detailed in Section 4.1.2.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

As detailed in the exclusion criteria, patients receiving nintedanib, full dose therapeutic anticoagulation or high dose antiplatelet therapy (e.g. acetyl salicylic acid >325 mg/day, or clopidogrel >75 mg/day, or equivalent doses of other antiplatelet therapy) are not eligible for participation in the study.

In case full-dose therapeutic anticoagulation or high-dose antiplatelet therapy is needed throughout the study, discontinuation of trial medication is highly recommended (see Section 3.3.4.1).

The use of nintedanib other than the investigational product is prohibited throughout the study, including the follow-up period (if any).

There are no restrictions for trial participants to receive vaccination for COVID-19 during or after study treatment period.

Cautionary notes

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Co-administration with oral doses of a potent P-gp and CYP3A4 inhibitors, e.g. ketoconazole, erythromycin, may increase exposure to nintedanib. In such cases, patients should be monitored closely. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with nintedanib.

Co-administration with oral doses of a potent P-gp and CYP3A4 inducers, e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort may decrease exposure to nintedanib and should be avoided.

For reasons given above, the use of potent P-gp and CYP3A4 inhibitors and inducers is restricted as shown in Table 4.2.2.1: 1.

Table 4.2.2.1: 1 Restrictions regarding use of potent P-gp and CYP3A4 inhibitors and inducers

P-glycoprotein (P-gp) and Cytochrome P450 3A4 (CYP3A4) inhibitors	
Ketoconazol, cyclosporine A (or ciclosporin), boceprevir, clarithromycin, conivaptan, erythromycin, indinavir, itraconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole.	NOT permitted: stop at least 7 days prior to PK sampling day until respective PK sampling is completed
P-gp and CYP3A4 strong inducers	
Avasimibe, carbamazepine, phenytoin, rifampin	NOT permitted: stop at least 7 days prior to PK sampling day until respective PK sampling is completed
Products including St. John's wort	NOT permitted: stop at least 7 days prior to PK sampling day until respective PK sampling is completed

As the most common side effects known for nintedanib are GI effects i.e. diarrhoea, nausea and vomiting (see Section 1.4.2) the concomitant use of medication with an overlapping safety profile (e.g. mycophenolate mofetil) should be carefully considered.

Nintedanib is also associated with increases in liver enzymes and bilirubin. If in addition to the trial medication, a treatment is introduced that is known to induce AST/ALT elevations (e.g. methotrexate, bosentan), additional measurements of liver enzymes (ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils) every 2 weeks for approximately 6 weeks, by using intermediate (a-visit) trial lab kit are recommended.

4.2.2.2 Restrictions on diet and life style

There are no restrictions on diet and life style.

4.2.2.3 Contraception requirements

The anti-angiogenic properties of nintedanib indicate a high potential for teratogenicity and embryotoxicity, including fetotoxicity and lethality.

WOCBP (for the definition please refer to Section 3.3.2) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly, in combination with one barrier method, from 28 days prior to initiation of study treatment, during treatment and until 3 months after last drug intake.

Contraception methods meeting these criteria are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on capsule counts, treatment compliance will be calculated as the number of capsules taken, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100, as shown below. Compliance will be verified by the Clinical Research Associate (CRA) authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of capsules actually taken} \times 100}{\text{Number of capsules which should have been taken as directed by the investigator}}$$

If the number of doses taken is not between 80-120%, site staff will explain to the patient and the parent(s)/legal guardian the importance of treatment compliance.

5. ASSESSMENTS

For the assessment of primary endpoints see Section 5.2 (assessment of safety) and Section 5.3 (drug concentration measures and pharmacokinetics).

5.1 ASSESSMENT OF EFFICACY

This Section describes the assessment of secondary and further endpoints of efficacy.

5.1.1 Assessment of FVC

Spirometry measurements will be performed according to ATS/ERS 2005 guideline [P05-12782]. Predicted normal values will be calculated according to GLI (Global Lung Initiative) [R15-0845] at each visit.

FVC will be assessed using standardised spirometry equipment which will be supplied to all participating sites. Spirometry equipment provided centrally will include pre-calibrated disposable flow sensors. These sensors demonstrate variability within the required standards of +/-3% determined by ATS/ERS 2005 guideline [P05-12782]. As such there is no need to conduct daily calibration prior to use, or the weekly linearity check. Mouthpieces suitable for the paediatric population will also be provided centrally.

Training will be given to ensure pulmonary function testing is properly conducted in the paediatric population.

Spirometry will be conducted while the patient is in a seated position. The test will be done in triplicate (three curves to be provided), and the best result selected according to the guidelines. The best of three efforts will be defined as the highest FVC, obtained on any of the three blows meeting the ATS/ERS criteria with preferably a maximum of five manoeuvres.

Efforts should be made to schedule the spirometric measurements at approximately the same time of the day, with reference to baseline measurement (Visit 2). On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Smoking (if applicable) should be discouraged throughout the visit days (clinic visit) and will not be permitted in the 30-minute period prior to spirometry. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odours (e.g. perfumes). If treated with bronchodilators, wash-out of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry.

Spirometry results will be electronically transmitted. To ensure the quality of endpoint measurement a central spirometry review is put in place to provide feedback to the investigational site, the CRA and the Clinical Trial Manager on the quality of the data received from the site.

Further instructions regarding FVC measurements will be provided in the ISF.

5.1.2 Assessment of SpO_2

Oxygen saturation (SpO_2) will be measured after minimum 5 minutes on room air by standard pulse oximetry at rest.

SpO_2 with exertion will be measured during the 6MWT. See Section 5.1.6 for details.

A pulsoximeter and sensors suitable for the paediatric population should be used. Forehead probe is recommended; if not available, earlobe and finger probe are also allowed; once chosen, the probe should be used consistently in the same patient.

Measurements will be recorded in source documents and transcribed into the CRF by designated site personnel.

5.1.3 Time to first respiratory-related hospitalization

Time to first respiratory-related hospitalization assessment will be based on the date of hospitalization collected on a specific hospitalization CRF page. The CRF page will capture whether the hospitalization was due to respiratory cause, and the primary admission diagnosis.

5.1.4 Time to first acute ILD exacerbation or death

Consistent with recent publication, acute exacerbation will be defined as significant worsening of the patient's respiratory condition that necessitates a change in regular management, based on more than 2 of the following criteria over 4 weeks [R19-0805]:

- Increase in respiratory rate ≥20% from baseline
- Increase in or development of dyspnoea
- Newly developing or increased abnormalities on chest imaging
- Onset/increase of oxygen demand to attain the individual baseline saturation (at rest and/or during exercise)
- Need for an additional level of ventilatory support (in addition to oxygen)
- Decrease in spirometry in children able to perform the tests (≥10%) from baseline for vital capacity
- Reduced exercise tolerance in children able to perform the tests (includes desaturation).

Events that are clinically considered to meet the definition of acute exacerbation but fail to meet the required criteria due to missing imaging data should be termed "suspected acute exacerbations".

For the endpoints evaluating the effect of nintedanib on these events, AEs reported by the Investigator will be used; the AEs will not be adjudicated.

5.1.5 Time to death

Time to death (all-cause mortality) will be based either on the date of death on the AE report for patients with AEs leading to death, or will be based on the information from the vital status assessment.

Analysis of time to death due to respiratory cause will be based on the adjudicated cause of death as determined by the Adjudication Committee (AC).

5.1.6 Six-minute walk test

Exercise capacity will be assessed conducting the 6-minute walk test (6MWT).

The 6MWT is a self-paced test of walking capacity. Patients are asked to walk as far as possible in 6 minutes along a flat corridor. The distance in metres is recorded. Standardised instructions and encouragement are commonly given during the test.

The 6MWT should be conducted as much as possible according to the methodology referred to in Appendix 10.5.

The 6MWT exhibits good test-retest reliability; however, there is strong evidence of a learning effect. At visits when the 6MWT is requested (see Flow Chart for details) the 6MWT will be conducted only once (not in duplicate). Training of site staff and patients before start of test at baseline (Visit 2) is important. Training materials and instructions will be provided in the ISF.

At visits when the 6MWT is requested the 6MWT should be preferably performed approximately at the same time of day to minimize intraday variability. Please refer to Section 6.2.2 for preferred order of completion of assessments during a clinic visit.

Prior to and at the end of the 6MWT, patients will be asked to rate their breathing discomfort and overall fatigue using the Borg CR-10 Scale® (see Appendix 10.6). During the test continuous pulse oximetry (SpO_2) will be performed.

The distance covered in 6 minutes, possible premature discontinuations and oxygen use, oxygen saturation measured by SpO_2, vital signs and symptoms of the patient will be recorded in the eCRF.

5.2 ASSESSMENT OF SAFETY

The primary and secondary endpoints of safety will be based on data at timepoints defined in Section 2.1.2 and Section 2.1.3. The 52 weeks time point will not be available for all patients, depending on the time of enrolment into the study.

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

The results must be included in the source documents available at the site.

All abnormal findings at baseline will be recorded on the Baseline Condition CRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate CRF page.

5.2.1.1 Body weight

Measurement of body weight will be performed at the time points specified in the Flow Chart. If possible, the patient's weight in the 2 years before screening (Visit 1) will be recorded, in order to detect any potential change in growth velocity over time.

Body weight measurements will be recorded in the source documents and transcribed into the CRF.

These measurements will be used to assess safety, and to assign the proper dose of trial medication at randomisation and subsequent IMP dispensing visits.

5.2.1.2 Height, leg length

Close monitoring of standing and sitting heights and leg length will be conducted at the time points specified in the Flow Chart and footnotes. If possible, the patient's height in the 2 years before screening (Visit 1) will be recorded, in order to detect any potential change in growth velocity over time.

At each time point, height, sitting height will be assessed three times, and the average of the 3 measurements will be taken. Height and sitting height will be assessed using a stadiometer. The stadiometer should be calibrated at regular intervals (see ISF for further instructions). The sitting height should be standardized and calibrated.
Leg length will be assessed by measuring the distance between the anterior iliac spine and the medial malleolus. This will be measured three times on each leg, and the average of the 3 measurements will be taken.

These measurements will be recorded in the source documents available at the site and the average transcribed into the CRF.

These measurements will be used to assess safety and be periodically reviewed by the Safety Monitoring Committee.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. See also Appendix 10.4 for details.

The results must be included in the source documents available at the site.

All abnormal findings at baseline will be recorded on the Baseline Condition CRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate CRF page.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points please see the Flow Chart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Patients do not have to be fasted for the blood sampling for the safety laboratory.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.
The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.7.1.1).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.7.1.4 and the DILI Checklist provided in the electronic Data Capture (eDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.
The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3: 1 Safety laboratory tests at regular site visits

The laboratory tests at regular site visits will include:

Category	Laboratory test
Haematology	Red blood cell count (RBC) Haemoglobin (Hb) Haematocrit (Hct) Mean corpuscular volume White blood cell count including differential count Platelet count
Biochemistry	Aspartate aminotransferase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase (ALK) Creatine kinase (CK) Lactate dehydrogenase (LDH) Total protein Total bilirubin Creatinine Glucose (non fasting, V1 and V2 only) Uric acid Thyroid stimulating hormone ß-HCG (at all visits requiring blood sampling for laboratory tests until EoT– in all and only female patients)*
Electrolytes	Sodium Potassium Calcium Chloride Inorganic phosphorus
Coagulation	International normalized ratio (INR) Activated partial thromboplastin time (aPTT) Prothrombin time (PT)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++)

*Pregnancy test is required in all female patients every 4-6 weeks, either at home or at site. ß-HCG test on blood will be conducted at all visits until end of treatment on blood collected for laboratory tests. Locally provided urine dipstick pregnancy tests will be dispensed for use between clinic visits starting from Visit 4. A urine dipstick pregnancy test will be conducted at the Follow-up Visit (if acceptable) and test results will be documented in the patient's records. In case of positive results, procedures defined in Section 5.2.7.2.3 should be followed.

Table 5.2.3:2 Safety laboratory tests at intermediate 'a'-visits

The laboratory tests at intermediate 'a'-visits will include:

Category	Laboratory test
Biochemistry	Total protein, creatinine, electrolytes and liver function (AST, ALT, GGT, alkaline phosphatase, and total bilirubin)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++)

At 'a-Visits', safety blood, and urine samples will be collected and submitted to the central laboratory if needed for additional safety monitoring at the discretion of the Investigator (see cautionary notes under Section 4.2.2.1 for additional safety monitoring).
The samples may be collected at the office of a local doctor using trial specific lab kits that will be sent to a central laboratory for analyses. These kits will be provided to patients at study visits as applicable.

A maximum total amount of approximately 38 mL blood will be taken for standard safety laboratory tests during the course of Part A. In Part B, a maximum total amount of approximately 44 mL blood will be taken for standard laboratory (this is based on a 76-week duration of Part B, but it might be less depending of the time the patient will stay in Part B).

Creatinine clearance will be calculated based on serum creatinine according to Schwartz formula [R10-0828, R11-4789] (see Appendix 10.2).

If laboratory values indicate abnormality, adequate and more frequent blood sampling may be performed at the discretion of the Investigator.

In case of liver function value elevations, close monitoring must be ensured by the Investigator. Refer to Section 4.1.2 for monitoring elevations and Section 3.3.4 for withdrawal criteria.

Laboratory analysis will be done using central laboratory services. Blood sampling will be conducted using materials and techniques suitable for the paediatric population. Venous whole blood will be collected in appropriate syringes provided by the sponsor through the assigned central laboratory. All efforts should be made to use the lowest amount of blood per sample as technically possible, e.g. by using special paediatric collection systems.

Details regarding centrifuge, processing, storage and shipment of samples will be determined by the central laboratory in accordance with the sponsor. The Investigators will be informed and instructed by the central laboratory and detailed documentation will be included in the ISF.

5.2.4 Electrocardiogram

Resting 12 lead Electrocardiograms (ECGs) will be conducted at sites using their own equipment.

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal (rate, rhythm and repolarization changes have to be evaluated, compared to previous tracings) and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Assessment of pathological findings of epiphyseal growth plate

MRI assessments of the distal femur and proximal tibia will be conducted as primary bone imaging methodology to assess the potential risk of skeletal toxicity of nintedanib in the growing population. In each patient the same side should be imaged at each assessment. In situations in which MRI cannot be performed, especially if sedation is required, x-rays of the distal femur and proximal tibia (AP knee radiograph) will be conducted as secondary methodology.

MRIs/x-rays of growth plates will be conducted in all patients who qualified for randomisation at baseline. Imaging follow-up will be conducted only in patients with open physes, at 3 months, 6 months, 9 months, 12 months after start of trial medication, and every 6 months thereafter until end of the study or closure of physes.

The same acquisition protocol specifications should be used for all MRIs/x-rays of growth plates. Details will be provided in the image acquisition guideline for bone safety monitoring available in the ISF. Whenever possible, scans should be completed on the same scanner and by the same radiologist at each site. Scans will be transferred for central review and stored at the sponsor facilities or by an external vendor.

MRI/x-ray assessments will be evaluated in a centralised manner by a blinded external expert in radiology. In addition, all MRI/x-ray assessments and height measurements (see Section 5.2.1.2) will be periodically reported to the Safety Monitoring Committee.

5.2.6 Assessment of pathological findings on dental examination or imaging

Dental examination (clinical examination) and imaging (panoramic x-ray) will be conducted in all patients who qualified for randomisation to assess the potential severe/irreversible effects of nintedanib on teeth in the study population.

Dental examination will be conducted at baseline. Follow-up will be conducted at 12 weeks, 24 weeks, 36 weeks, 52 weeks after start of trial medication, and every 24 weeks thereafter until end of the study.

A panoramic x-ray will be conducted at baseline. Dental imaging follow-up will be conducted at 24 weeks, 52 weeks after start of trial medication, and every 48 weeks thereafter until end of the study.

Dental examination will be conducted at the investigational site or external facility by a dentist.

Panoramic x-rays will be conducted at the investigational site or external facility.
The same specifications will be used for all panoramic x-rays. Details will be provided in the image acquisition guideline for teeth safety monitoring available in the ISF. Whenever possible, panoramic x-rays should be completed on the same device. Dental cone beam computed tomography can be conducted only in case panoramic x-rays cannot be performed, as far as it allows the same assessments, it is conducted according to the image acquisition guideline, and the same device is used consistently in the same patient.

X-rays will be transferred for central review and stored at the sponsor facilities or by an external vendor.

Panoramic x-rays will be evaluated in a centralised manner by a blinded external expert in paediatric dentistry.

Dental examination and imaging will be periodically reported to the Safety Monitoring Committee.

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of AEs

5.2.7.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease (including acute ILD exacerbations) or of other pre-existing conditions;
- Pathological findings of epiphyseal growth plate on imaging;
- Pathological findings on dental examination or imaging;

- Changes in vital signs, ECG, physical examination (including changes in standing and/or sitting height, changes in leg length) and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.7.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.7.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.
The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described above.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.7.2, subsections “AE Collection” and “AE reporting to sponsor and timelines”**.**

5.2.7.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor’s Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.7.2.2.

The following are considered as AESIs:

- adverse events relating to gastrointestinal perforation
- bleeding
- hepatic injury
- pathological findings identified on bone imaging
- stunted growth identified on dental imaging

Hepatic injury

In this trial protocol, signs of hepatic injury are defined as:

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN*
- ALT and/or AST ≥3 fold ULN and unexplained INR > 1.5*
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)*
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

*in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to immediately stop the trial medication and be followed up according to the "DILI checklist" provided in the eDC system. The investigator is asked to collect requested information within 48 hours upon laboratory hepatic injury alert/notification.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.7.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate:	Sufficient discomfort to cause interference with usual activity.
Severe:	Incapacitating or causing inability to work or to perform usual activities.

The intensity (severity) of diarrhoea adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 [R18-1357], Table 5.2.7.1.5: 1.

Table 5.2.7.1.5: 1 CTCAE Categorization for diarrhoea

CTCAE Grade	**Diarrhoea**
1	Increase of <4 stools per day over baseline
2	Increase of 4 to 6 stools per day over baseline
3	Increase of ≥7 stools per day over baseline; incontinence
4	Life threatening consequences
5	Death

5.2.7.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.7.2 Adverse event collection and reporting

5.2.7.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.7.2.2), but not on the CRF.

Vital Status Data Collection

Patients who discontinue trial medication prematurely, whose parents/legal guardians agree to be contacted further but do not agree to physical visits, should be followed up as described in Section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, and trial treatment related SAEs and trial treatment related AESIs the investigator becomes aware of.

5.2.7.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.7.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.7.2.4 Safety monitoring and adverse events with additional information collection

- A blinded external expert in radiology will review all MRI/radiological assessments (bone imaging).
- A blinded external expert in paediatric dentistry will review all panoramic x-rays (dental imaging).
- An independent Safety Monitoring Committee (SMC) will conduct regular reviews of the trial safety data, with access to any data including MRI/radiological assessments, height measurements, and panoramic x-rays, as detailed in Section 3.1, in Section 5.2.5 and in the SMC charter.
- An independent Adjudication Committee (AC) will review all fatal cases and adjudicate all deaths to either cardiac, respiratory or other causes and will review all adverse events categorized as major adverse cardiovascular events (MACE). MACE is defined as non-fatal myocardial infarction, non-fatal stroke and cardiac death.
- Additional details (on top of standard AE and SAE reporting) will be collected in the eCRF for the adverse event 'diarrhoea' and the adverse events in the subordinate Standard MedDRA Query (SMQ) 'Haemorrhage terms, excluding laboratory terms'.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Pharmacokinetics will be one primary endpoint of this study. For this reason extensive PK sampling is planned, which is considered appropriate for the targeted age range of ≥6 years. In exceptional cases of paediatric patients aged <12 years a sparse sampling approach should be applied; for details refer to the Flow Chart for PK blood sampling.

PK plasma sampling will be conducted at Visit 3 and Visit 7 at steady state, just before drug administration and 1h, 2h, 3h, 4h, 6h, 8h post-dose (see Flow Chart for PK blood sampling).

In rare circumstances PK sampling might need to be repeated (e.g. blood samples not taken at required timepoint, wrong medication taken in the days before PK sampling or on the day of PK sampling, destroyed/lost sample during shipment). In such cases PK sampling will be repeated close before the end of treatment visit, to allow the maximum possible interval from the previous PK sampling.

Based on this PK sampling, the area under the plasma concentration-time curve at steady state ($AUC_{\tau,ss}$) and further PK parameters (see Section 2.2.2) will be calculated by non-compartmental analyses. The pharmacokinetic parameters will be included in the clinical trial report. In addition, population pharmacokinetics analyses will be conducted to further characterize PK (see Section 7.2.6), which will be reported separately.

5.3.2 Methods of sample collection

A detailed description of sample collection and handling is provided in the laboratory manual. For quantification of drug plasma concentrations of nintedanib, venous blood will be collected using a pre-labelled potassium ethylenediamine-tetraacetic acid (EDTA) containing blood drawing tube.

5.3.3 Analytical determinations

Nintedanib (in form of its free base BIBF 1120 BS) plasma concentrations will be determined by a validated assay based on liquid chromatography-tandem-mass spectrometry (LC-MS / MS). The procedures and specifications of the analytical method are available at the bioanalytical site (Nuvisan GmbH & Co KG, Wegenerstraße 13, 89231 Neu-Ulm, Germany).

5.4 ASSESSMENT OF BIOMARKERS

[redacted]

5.4.2 Pharmacogenomics biomarkers

n.a.

[redacted]

5.5 BIOBANKING

n.a.

5.6 OTHER ASSESSMENTS

5.6.1 Assessment of quality of life via PedsQL™

Health-related quality of life will be assessed using the PedsQL™ questionnaire [R19-0760].

The PedsQL™ questionnaires will be administered according to the PedsQL™ Administration Guidelines^{SM} (for questionnaires to be administered in the different age groups and the administration guidelines see Appendix 10.7).

The PedsQL™ should be completed in a quiet area/room *before* the respondents complete any other health data forms and *before* they see the investigator.

Parents, Children (8-12 year-old) and Teens (>12 year-old) may self-administer the PedsQL™ targeted for their age group after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen. For the Young Child (<8 year-old), the PedsQL™ should be administered by reading the instructions and each item to the young child word for word.

If during the trial a patient changes age group, then the questionnaire appropriate for that age group should be administered.

If a patient has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the patient (e.g., administering the Young Child (5-7) Self-Report version with the three faces response choices to an 8 year-old). However, if a patient presents with severe cognitive impairments (as determined by the administrator), the PedsQL™ may not be appropriate for that patient. In such cases, only the Parent-Proxy Report should be administered to the patient's parent.

The parent and the patient must complete the questionnaires independently of one another. Consulting with one another during the completion of the questionnaire should be discouraged. The patient answering the questionnaire should be facing away from the parent.

The parent and the patient will be provided with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. The administrator will remain nearby should questions or concerns arise.

If the patient or parent has a question about what an item means or how they should answer it, the administrator should not interpret the question for them, just repeat the item to them verbatim, ask them to answer the item according to what they think the question means and choose the response that comes closest to how they feel. The patient and/or the parent has the option of not answering a question if they truly do not understand the question.

When the parent/patient returns the PedsQL™, the administrator will look it over, check to see that all answers have been completed and verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, the administrator will ask the parent or patient to indicate their response.

The responses will be transcribed into the CRF by designated site-personnel.

For further instructions and details see Appendix 10.7.

[redacted]

5.6.3 Patient's acceptability of the investigational product based on the size and number of capsules

Acceptability is defined as the overall ability and willingness of the patient to use the medicinal product as intended.

In this study acceptability of the investigational product based on the size and number of capsules will be assessed.

The assessment of acceptability will be performed by the patient using the acceptability questionnaire for the patient. If the patient is considered not old enough per investigator judgment, the parent/caregiver can assist with completion of the questionnaire (see Appendix 10.8 for details).

In between study visits, the parent/legal guardian will be asked to record any failed or missed intake of medication (e.g. the patient did not swallow the medication, or doses were missed, etc.) and provide this documentation to the investigator at the next study visit. The parent/legal guardian will be instructed to inform the investigator immediately if two or more consecutive doses of trial medication are missed or not taken correctly.

Moreover, to collect the investigator / site staff impression about the patient's acceptability of the study medication intake, the treatment acceptability questionnaire for the investigator or investigational site staff will be completed by the investigator / site staff (see Appendix 10.8 for details).

5.6.4 Assessment of D_{LCO}

The diffusing capacity of the lung for carbon monoxide (D_{LCO}) will be assessed at Visit 2 to characterize the patient.

Single-breath D_{LCO} measurement will be carried out according to the ATS/ERS guideline on D_{LCO} measurements [R06-2002] using the site own equipment. Before beginning the test, the manoeuvres should be demonstrated and the subject carefully instructed.

D_{LCO} will be measured at Visit 2 and corrected for haemoglobin (Hb) measured at Visit 1 (see Appendix 10.3 for details).

D_{LCO} values will also be adjusted for altitude and carboxyhaemoglobin (COHb). For predicted normal values, different sites may use different prediction formulas, based on the method used to measure D_{LCO}. In any case, the calculation method used must be in compliance with the ATS/ERS guideline on D_{LCO} measurements [R06-2002] and the prediction formula appropriate for that method. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

The D_{LCO} assessment should be performed after the FVC measurement.

5.6.5 Fan severity score

Physician reported Fan severity score [R09-5337] at Visit 2 will be used to determine eligibility of the patient. For instructions on how to assign the severity-of-illness score see Appendix 10.1.

The score used to determine eligibility of the patient can be based on historical data. Documentation of measurements used to determine the score at Visit 2 (e.g. ambulatory oxygen saturation or night time oximetry reports) will need to be documented and made available for central review. Data from study visit procedures (e.g. ambulatory oxygen saturation) can also be used.

Fan score as an outcome measure will be calculated by the sponsor based on response to Borg CR-10 scale® and oxygen saturation at rest and after 6-minute walk test. This will be further defined in TSAP.

5.6.6 Assessment of HRCT

HRCT assessment of presence of fibrosis has become an essential part of the evaluation and diagnosis of patients with paediatric fibrosing ILDs.

Screening HRCT will be used in all patients to determine study eligibility. Central review of the screening HRCT images will ensure that relevant lung fibrosis is present.

In addition to confirmation of the presence of relevant fibrosis, visual and potentially quantitative analyses of the screening HRCTs might be performed to explore potential predictors of clinical outcomes e.g. FVC decline, progression, exacerbation.

The same acquisition protocol specifications will be used for all screening HRCT scans, and should be followed when possible. Details will be provided in the image acquisition guideline available in the ISF. Scans will be transferred for central review. HRCT scans might be stored for up to 30 years at the sponsor facilities or by an external vendor for future scientific research.

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted for the assessment of endpoints in this study are using standard methods. Some measurements might be new methodologies already used in clinical trials but not yet validated for this rare disease.

Refer to Section 1.4.2 for the discussion of the benefit-risk of monitoring the potential impact of the investigational treatment in bone development and growth, as well as in dentition.

The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used as measurements to assess drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of a screening period (from informed consent to Visit 2), a treatment period divided into double blind Part A of 24 weeks (from Visit 2 to Visit 6) and open label Part B of variable duration (from Visit 6 to EoT), and a follow-up period (from EoT to End of trial visit; this period is only for those patients who are not enrolled into the separate open label extension study).

If additional PK data are needed after DBL 1, patients meeting in-/exclusion criteria at Visit 2 will be directly entered into Part B, and patients undergoing double blind treatment will be directly switched to Part B.

All study visits should be scheduled according to the visit schedule defined in the Flow Chart. Windows of ±3 days for Visits 3 to 7, ±7 days for the following visits are defined to accommodate scheduling problems.

All efforts should be made to perform all visits as requested.

If a delay is observed for a particular visit, the original calendar schedule should be kept for subsequent visits (delays should not accumulate).

In case of a missed visit the investigator should contact the sponsor; these situations will be addressed on a case by case basis. Should a visit be postponed until the time window of the next visit, the visit will be skipped and the next visit will be scheduled as defined by Flow Chart, based on the actual date of Visit 2.

Timing of visits should also be properly planned, taking into account that:

- The patient should take the trial medication twice daily, at about the same time every day (between 06:00 and 11:00 in the morning, 18:00 and 23:00 in the evening), with a dose interval of approximately 12 hours from one dose to the next dose. The morning dose at Visit 2, Visit 3, Visit 6 and Visit 7 should be taken at the site.
- The pre-dose PK sampling (Visit 3 and Visit 7) should be conducted immediately before intake of the morning dose of trial medication; the post-dose PK sampling should be conducted 1h, 2h, 3h, 4h, 6h, 8h after the morning dose of trial medication.
- Spirometric measurements should always be conducted at approximately the same time of the day, with reference to baseline measurement (Visit 2).

In the event of force majeure or other disruptive circumstances (e.g. pandemic) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient's parent(s)/legal guardian (and assent by the patient where applicable), sponsor and investigator may implement risk mitigation measures and modifications to CTP standard procedures which may include, but are not limited to, direct-to-patient shipment of trial medication from the site, laboratory tests done by local physician/local lab (if possible samples collected and processed by local physician/local lab using kits provided by central laboratory and sent to central laboratory for analyses), bone and dental assessments (bone

imaging, dental imaging, oral examination) done at local facilities, home visits by site staff or trained healthcare provider (e.g. nurse) that could be combined with remote patient visits (via telephone and/or internet based means of communication). Risk mitigation measures and modifications to CTP standard procedures that can be implemented at a site are described in Appendix 10.9. Measures implemented at a site should be mentioned in the information leaflet for the patient's parent(s)/legal guardian (and in the patient information where applicable). The implementation of these measures will depend on consent from the patient's parent(s)/legal guardian, operational feasibility, local law and regulations. If alternative procedures are implemented, the deviations from the standard trial procedures will be precisely documented and the implications considered for the analysis of the trial data. If the defined minimum frequency of trial procedures cannot be adhered to, discontinuation from trial medication should be considered. See Appendix 10.9 for details.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Trial procedures and observations will be completed at study visits according to the Flow Chart and instructions given in the Flow Chart footnotes as well as in Sections 6.2.1, 6.2.2, 6.2.3. Explanations of procedures and observations are given in Section 5.

Before start of each visit the investigator and site personnel involved in the conduct of the study should carefully prepare what is needed for the conduct of the visit, taking into account the specific structure of the site and the mandatory needs outlined in the clinical trial protocol. Efforts should be made to ensure the well-being of the patient during the visit.

6.2.1 Screening

Informed consent (before or at the latest at Visit1)

- Informed consent (and assent where applicable) will be obtained before any procedure related to the study, including HRCT transfer to central review.
- A preliminary check of in-/exclusion criteria is recommended at time of informed consent to avoid unnecessary wash-out procedures in non-eligible patients.

Upon obtaining informed consent:

- Site personnel will perform a screening call/notification in IRT to register patient's screening (date of call/notification will be automatically captured) and ensure timely availability of trial medication.
- The patient will receive a trial identification card.
- Patient and parent(s)/legal guardian will be instructed on procedures to be followed until the next study visit.
- An HRCT not older than 12 months will be evaluated by the investigator and sent for central review if meeting criteria defined in Section 3.3.2.1. If the patient does not have an HRCT within 12 months from the time of the scheduled Visit 1, or the available HRCT does not meet the image acquisition specifications of the study (see image acquisition guideline available in the ISF), the HRCT can be performed for the purposes of participation in the trial provided the patient meets eligibility criteria that can be assessed at that timepoint.

- If available, a lung biopsy will be evaluated by the investigator and sent for central review if meeting criteria defined in Section 3.3.2.1.
- In patients without any documented lung biopsy, or whose biopsy results do not meet the criteria listed in Section 3.3.2.1, a second HRCT will be evaluated by the investigator and sent for central review if meeting criteria defined in Section 3.3.2.1.

[redacted]

Visit 1 (Screening)

Observations and procedures:

- If informed consent was not collected at a separate visit, obtaining informed consent (and assent where applicable) and the above listed procedures will be done prior to any further procedure at this visit.
- If not done at a separate visit, site personnel will perform a screening call in IRT to register patient's screening (date of call/notification will be automatically captured) and ensure timely availability of trial medication.
- Demographics will be recorded.
- Medical history including pre-existing conditions will be recorded.
- Concomitant therapy including previous medications will be recorded.
- Any adverse events (since consent, if applicable) will be recorded.
- Prior to blood draw, physical examination including vital signs, weight, height (standing and sitting) will be performed; data will be recorded in source documents and timely transferred per instructions provided (see ISF), to ensure central review as needed.
- If possible prior to blood draw, a 12-lead ECG at rest will be conducted with the site's own equipment and evaluated by qualified personnel at site.
- SpO_2 measurement will be conducted on room air at rest.
- FVC measurement will be conducted with the spirometer provided by the sponsor, according to procedures defined (see ISF for details).
- Blood and urine samples (safety laboratory tests, and pregnancy test on serum in female patients only) will be collected and submitted to the central laboratory (for details refer to Section 5.2.3 and instructions given in the ISF). Prior to blood draw a pre-assessment of all in-/exclusion criteria is highly recommended to avoid unnecessary blood draws.
- HRCT will be done (if needed) and sent to central review by site personnel (if not done before).
- Biopsy will be sent to central review by site personnel (if needed and not done before).
- An interim check of in-/exclusion criteria will be done.
- If the patient qualifies to enter the screening period, Visit 2 will be scheduled; patient and parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.

6.2.2 Treatment period

The following has to be ensured during trial visits according to the study Flow Chart:

- The PedsQL™ questionnaire must be always administered prior to any other procedures, and according to instructions given (see Section 5.6.1 and Appendix 10.7).
- Blood draw for laboratory tests must be performed prior to administration of trial medication (applicable to Visit 2 and Visit 6 only; for the timing of blood draws to be conducted at Visit 3 and Visit 7 please refer to the Flow Chart for PK blood sampling).
- FVC measurements at all visits should be performed approximately at the same time of the day to reference time point at Visit 2.
- Order of pulmonary function tests at Visit 2 must be:
  1. FVC measurement with the spirometer provided, followed by patient's rest
  2. D_{LCO} measurement with site's own equipment.

Visit 2 (baseline)

For the conduct of Visit 2 the following prerequisites must be met:

- Confirmation of fibrosing ILD based on HRCT central review (and biopsy central review if needed).
- Safety laboratory results from blood sampling conducted at Visit 1, including haemoglobin and creatinine measurements, have been provided and are available at the site.

If for any reason the screening phase for an individual patient lasts for more than 6 weeks, then the laboratory examination for Visit 1 has to be repeated before randomization. The screening phase (from informed consent until Visit 2) must be no longer than 12 weeks.

Observations and procedures:

- PedsQL™ questionnaire will be administered prior to any other procedures and checked for completeness (see Section 5.6.1 and Appendix 10.7).
- Adverse events, any ILD exacerbations, respiratory-related hospitalizations [redacted], and concomitant therapy since last visit will be reviewed and recorded.
- Prior to blood draw, physical examination including vital signs, weight, height (standing and sitting), and leg length will be performed; data will be recorded in source documents and timely entered into the eCRF.
- If the ECG was abnormal at Visit 1, the 12-lead ECG at rest will be repeated (if possible prior to blood draw), and evaluated by qualified personnel at site.
- SpO_2 measurement will be conducted on room air at rest.
- FVC measurement will be conducted according to procedures defined (see ISF for details).

- D_{LCO} measurement will be conducted after FVC measurement and patient's rest. D_{LCO} will be corrected for haemoglobin (Hb) measured at Visit 1 (see Section 5.6.4 for details).
- The 6-minute walk test including Borg CR-10 scale® and continuous pulse oximetry (SpO_2) will be conducted per instructions given in Section 5.1.6.
- All in/exclusion criteria will be checked, and if all in-/exclusion criteria are fulfilled the patient will qualify for the treatment period of the study.
- Blood and urine samples (safety laboratory tests, and pregnancy test on serum in female patients only) will be collected and submitted to the central laboratory.

[redacted]

- If a patient is eligible for the trial, randomization will be performed by using the IRT system.
- The assigned trial medication will be administered at the site. Medication wallets will be dispensed, patients and parent(s)/legal guardian will be properly instructed about how and when the study medication should be taken until the next visit. The parent(s)/legal guardian (and the patient, where applicable based on the patient's age) will be properly instructed to contact the site in case of adverse events (details given in the informed consent, and assent where applicable).
- A PK diary card will be dispensed; the patient and parent(s)/legal guardian will be instructed on how it should be completed in the 3 days before the next visit.
- The next visit will be scheduled; patient and parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.
- An MRI of epiphyseal growth plates will be conducted* in all patients who qualified for randomisation according to protocol requirements (see Section 5.2.5). If MRI cannot be performed, an x-ray will be conducted. The MRI (or x-ray) will be sent to central evaluation by radiology expert on a timely manner.
- Dental examination will be conducted* in all patients who qualified for randomisation according to protocol requirements (see Section 5.2.6), and evaluated at site.
- Dental imaging will be conducted* in all patients who qualified for randomisation according to protocol requirements (see Section 5.2.6). The panoramic x-ray will be sent to central evaluation by a paediatric dentistry expert in a timely manner.

*If it's not possible to conduct this procedure on the day of the visit, the procedure can be done in the 2 weeks immediately after the visit (please refer to the image acquisition guideline available in the ISF for details).

[redacted]

If by the end of Visit 2 the patient does not qualify for randomization, screening failure will be notified via IRT. Patient rescreening at a later date is possible. At due time a new informed consent (and assent where applicable) will be collected; site personnel will perform a re-screening call/notification in IRT to register patient's re-screening; the patient will be assigned a new patient number which will be linked to the original patient number, and

complete all study procedures according to Flow Chart. Re-screening of a previously screen failed patient will be permitted once.

Results of laboratory examination of samples collected at Visit 2 will become available only after Visit 2. Since laboratory results from Visit 2 cannot be used to assess patient's eligibility, laboratory results from Visit 1 will be used instead. In case laboratory results of Visit 2 meet any exclusion criterion, the investigator must discuss the case with the sponsor, and obtain directions whether or not the patient should discontinue trial medication. The patient's conditions and the decision taken should be properly documented, reason for continuation should be justified in writing by the investigator.

Visit 3 and Visit 7 (visits with extensive PK)

For the conduct of Visit 3 and Visit 7 extensive PK the following prerequisites must be met:

- The patient has taken the trial medication in the three days preceding the visit as instructed.

If PK sampling needs to be repeated (see Flow Chart for PK blood sampling and Section 5.3.1 for details), PK sampling will be repeated close before the end of treatment visit, to allow the maximum possible interval from the previous PK sampling.

Observations and procedures:

- The site personnel will check the PK diary card and confirm that the trial medication has been taken in the three days preceding the visit. If this is not confirmed, the visit will be rescheduled.
- Criteria for dose reduction / interruption will be checked, if any.
- The pre-dose PK sample will be taken immediately before drug administration, study medication will be administered, and post-dose PK samples will be taken at timepoints defined (see Flow Chart for PK blood sampling for details). Date and exact clock time of drug administration and blood sampling must be recorded in the eCRF.
- After administration of trial medication, the patient's acceptability questionnaire will be administered (Visit 3 only).
- Compliance will be checked and drug accountability will be completed (Visit 3 only; at Visit 7 drug accountability is to be completed only in case of dose reduction / increase).
- Adverse events, any ILD exacerbations, respiratory-related hospitalizations [redacted], and concomitant therapy since last visit will be reviewed and recorded.
- Physical examination including vital signs and weight (the latter Visit 3 only) will be performed; data will be recorded in source documents and transferred as instructed.
- SpO_2 measurement will be conducted on room air at rest.
- FVC measurement will be conducted according to procedures defined (see ISF for details).
- Blood and urine samples (safety laboratory tests, and pregnancy test on serum in female patients only) will be collected and submitted to the central laboratory.

- New medication wallets will be assigned by using the IRT system and dispensed, returned wallets will be collected as instructed (see ISF for details) (Visit 3 only).
- The next visit will be scheduled; patient and parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.

Visits 4, 5, 6, 8, 9, X (treatment period)

Observations and procedures:

- PedsQL™ questionnaire will be administered prior to any other procedures and checked for completeness (Visit 6 and Visit 9 only).
- Compliance will be checked and drug accountability will be completed.
- Criteria for dose reduction / interruption will be checked, if any.
- The site personnel will check the pregnancy test diary card (females only, and not to be done at Visit 4) and confirm that since the last scheduled visit at the site the pregnancy test has been repeated every 4-6 weeks until the current visit. If not confirmed, the investigator will re-instruct the patient and parent(s)/legal guardian. Test results will be documented in the patient's records. In case a positive test is reported the sponsor should be contacted immediately. Refer to Section 3.3.4.1 for further instructions. Refer to Section 5.2.7.2.3 for detailed information on event reporting in case of pregnancy.
- Adverse events, any ILD exacerbations, respiratory-related hospitalizations [redacted] and concomitant therapy since last visit will be reviewed and recorded.
- Prior to blood draw, physical examination including vital signs, weight, height, and leg length will be performed (height and leg length not planned at Visit 4; leg length planned every 24 weeks after the first year); data will be recorded in source documents and timely transferred per instructions provided (see ISF), to ensure central review as needed.
- The 12-lead ECG at rest will be conducted (if possible prior to blood draw), and evaluated by qualified personnel at site (Visit 6, Visit 9 and every 24 weeks after the first year only).
- SpO_2 measurement will be conducted on room air at rest.
- FVC measurement will be conducted according to procedures defined (see ISF for details).
- The 6-minute walk test including Borg CR-10 scale® and continuous pulse oximetry (SpO_2) will be conducted (Visit 6 and Visit 9 only).
- Blood and urine samples (safety laboratory tests, and pregnancy test on serum in female patients only) will be collected and submitted to the central laboratory.

[redacted]

- New medication wallets will be assigned by using the IRT system and dispensed, returned wallets will be collected as instructed (see ISF for details).
- Visit 6 only: The first dose of the open label trial medication will be administered at the site.
- Visit 6 only: The patient's acceptability questionnaire will be administered.

- Visit 6 only: a PK diary card will be dispensed; the patient and parent(s)/legal guardian will be instructed on how it should be completed in the 3 days before the next visit. If PK sampling needs to be repeated (see Flow Chart for PK blood sampling and Section 5.3.1 for details), the PK diary card will be dispensed during the visit before PK sampling, and the patient will be instructed as needed.
- Urine dipstick pregnancy tests and a pregnancy test diary card will be dispensed (females only); the patient and parent(s)/legal guardian will be instructed on how the test should be conducted, and the diary should be completed, until the next visit.
- The next visit will be scheduled; patient and parent(s)/legal guardian will be instructed on procedures to be followed until the next visit. In preparation to Visit 6 the patient and parent(s)/legal guardian will be instructed that on the day of this visit the morning dose of trial medication should not be taken before going to the site, because the morning dose will be taken during the visit.
- Follow-up MRIs (or x-rays if baseline MRI was not possible) of epiphyseal growth plates will be conducted* - in patients with open physes only - at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter, until the end of the study or closure of the physes. MRIs (or x-rays) will be sent to central evaluation by radiology expert on a timely manner.
- Follow-up dental examination will be conducted* in all patients at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter until the end of the study.
- Follow-up dental imaging will be conducted* in all patients at 24 weeks, 52 weeks and every 48 weeks thereafter until the end of the study. Panoramic x-ray will be sent to central evaluation by paediatric dentistry expert on a timely manner.

*If it's not possible to conduct this procedure on the day of the visit, the procedure can be done in the week immediately before or after the visit (please refer to the image acquisition guideline available in the ISF for details).

[redacted]

End of Treatment Visit

Patients who discontinue trial treatment prematurely will undergo the End of Treatment (EoT) visit as soon as possible, and complete procedures defined (see Flow Chart and Section 3.3.4). The first visit after the EoT visit will be skipped if the EoT visit occurs within 4 weeks prior to the scheduled visit.

Patients who did not discontinue trial treatment prematurely should undergo the EoT visit as soon as the timing of final DBL (DBL 2) and EoT visit has been communicated (see Section 3.1 for details). If a regular study visit is scheduled in the period when the EoT visit should be conducted, all procedures required at this regular study visit and the additional procedures, if any, required at the EoT visit will be conducted during the same visit.

If the initiation of the open label extension trial is supported by the benefit-risk assessment from DBL 1, patients who completed the treatment period according to protocol will be offered participation in a separate open label extension trial. When the End of Treatment Visit is planned, the Investigator or delegated personnel should discuss with the patient and

the patient's parent(s)/caregiver about recruitment into the open label extension trial. The discussion should be documented and the information will be collected via eCRF. A separate informed consent/assent for the participation in the open label extension trial will be collected as part on the open label extension trial procedures.

If the initiation of the open label extension trial is not supported, patients will complete the EoT visit and be asked to attend a follow-up visit (see Section 6.2.3 for details).

At the EoT visit the site personnel will perform a call in IRT to register patient's end of treatment. Returned wallets will be collected as instructed (see ISF for details).

Dose reduction visit / dose increase visit

If a patient experiences a drug related adverse event, the dose can be reduced and the dose can be re-increased after recovery as described in Section 4.1.2.

If the dose change does not occur in concomitance to a scheduled visit, the patient will attend an unscheduled visit at the site.

The following procedures will be completed:

- Compliance will be checked and drug accountability will be completed.
- Criteria for dose reduction will be checked, if any, and recorded.
- Adverse events, any ILD exacerbations, respiratory-related hospitalizations [redacted] and concomitant therapy since last visit will be reviewed and recorded.
- Prior to blood draw, physical examination including vital signs and weight will be performed.
- Blood and urine samples (safety laboratory tests, and pregnancy test on serum in female patients only) will be collected and submitted to the central laboratory.
- New medication wallets will be assigned by using the IRT system and dispensed, returned wallets will be collected as instructed (see ISF for details).

Intermediate 'a-Visits'

During the treatment period intermediate lab tests ("a"-Visits) for safety monitoring may be conducted, as needed at the discretion of the investigator or as recommended by the SMC.

Blood and urine samples will be collected and submitted to the central laboratory for analysis. Samples may be collected locally (e.g. by the general practitioner or a nurse). The Investigator or site personnel will give the parent(s)/legal guardian (or the patient, depending on the age), written instructions and procedures to be followed, together with the trial lab kits for the respective 'a-Visit' to be used for collecting and shipping samples to the central laboratory.

Intermediate pregnancy tests

During the treatment period and the follow-up period a pregnancy test must be conducted in all female patients every 4-6 weeks.

Pregnancy test will be conducted on blood collected at every visit until end of treatment. Urine dipstick pregnancy test kits will be provided locally for use between visits when visit intervals are >6 weeks. Test results must be documented in the patient's pregnancy test diary card and transferred to the patient's records at the next site visit.

6.2.3 Follow-up period and trial completion

Follow-up Visit

A Follow-up Visit should be conducted 28 days (+3 days) after the end of treatment in all patients who are not enrolled into the separate open label extension trial.

Observations and procedures:

- Adverse events, any ILD exacerbations, respiratory-related hospitalizations, and concomitant therapy since last visit will be reviewed and recorded.
- Physical examination including vital signs will be performed; weight and height will be repeated at follow-up in case of clinically relevant changes at EoT; data will be recorded in source documents and timely transferred per instructions provided (see ISF), to ensure central review as needed.
- Blood and urine samples will be repeated at follow-up in case of clinically relevant changes at EoT, unless the patient is enrolled into the open label extension trial.
- Pregnancy test on urines will be conducted in female patients only. Test results will be documented in the patient's records.
- Patient's participation will be concluded for patients with withdrawn consent (and/or assent as applicable) and do not attend future visits.

Trial completion

The trial completion CRF page must be filled-in when the patient has terminated the trial. The end of the trial for the individual patient is:

- For patients who have completed the study visits as scheduled and are enrolled into the separate open label extension trial, end of trial is at EoT.
- For patients who have completed the study visits as scheduled and are NOT enrolled into the separate open label extension trial, end of trial is at the follow-up visit.
- For patients who have NOT completed the study visits as scheduled and withdraw consent:
  - If consent withdrawal occurs at time of trial medication discontinuation, end of trial is at EoT visit followed by the follow-up visit.
  - If consent withdrawal occurs after EoT was already completed, then the patient should have a final visit based on their scheduled study visit.

After completion of the trial, patients who are enrolled into the open label extension trial will have access to treatment with nintedanib.

Patients who prematurely discontinued trial medication

In case a patient has permanently discontinued trial medication, for whatever reason, at the End of Treatment visit the patient will be encouraged to attend all future visits (except 'a-Visits') up to the end of trial as originally planned.

During these visits the patient will undergo the following observations and procedures:

- PedsQL™ questionnaire will be administered prior to any other procedures and checked for completeness (Visit 6 and Visit 9 only).
- Adverse events, any ILD exacerbations, respiratory-related hospitalizations [redacted] and concomitant therapy since last visit will be reviewed and recorded.
- Physical examination including vital signs, weight, height, and leg length will be performed (height and leg length not planned at Visit 4; leg length planned every 24 weeks after the first year); data will be recorded in source documents and timely transferred per instructions provided (see ISF), to ensure central review as needed.
- SpO_2 measurement will be conducted on [redacted]oom air at rest.
- FVC measurement will be conducted according to procedures defined (see ISF for details).
- The 6-minute walk test including Borg CR-10 scale® and continuous pulse oximetry (SpO_2) will be conducted (Visit 6 and Visit 9 only).

[redacted]

- The next visit will be scheduled; patient and parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.
- Follow-up MRIs (or x-rays if baseline MRI was not possible) of epiphyseal growth plates will be conducted* - in patients with open physes only - at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter, until the end of the study or closure of the physes. MRIs (or x-rays) will be sent to central evaluation by radiology expert on a timely manner.
- Follow-up dental examination will be conducted* in all patients at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter until the end of the study.
- Follow-up dental imaging will be conducted* in all patients at 24 weeks, 52 weeks and every 48 weeks thereafter until the end of the study. Panoramic x-ray will be sent to central evaluation by paediatric dentistry expert on a timely manner.

*If it's not possible to conduct this procedure on the day of the visit, the procedure can be done in the week immediately before or after the visit (please refer to the image acquisition guideline available in the ISF for details).

These visits will be regarded as part of the trial despite the patient having discontinued trial medication.

The need for coming to future visits in case of prematurely discontinuation of trial medication will be explained to patients and parent(s)/legal guardian prior to start of trial participation.

Vital status information

In case of premature discontinuation of trial medication, if the patient does not attend future visits as planned, every attempt will be made to get information on vital status at 24 weeks after randomization, i.e. at the time of data cut-off for the primary analysis, at 52 weeks and at the end of the trial.

Permission to further contacts by site personnel, e.g. by telephone calls, to allow collection of the vital status must be given in the informed consent.

Collection of vital status will be performed in accordance with national ethical and regulatory guidelines.

If death occurs, the investigator will review the circumstances, including the relevant medical records, to ascertain the most likely primary and secondary causes of death. The cause of death will be adjudicated by the AC.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The main objective will be assessed by calculating descriptive statistics for safety endpoints and by exploratory PK analyses. The PK, safety and efficacy endpoints as well as other assessments as stated in Section 5, will be compared between the treatment groups using descriptive statistics.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory testing is performed and hence no null and alternative hypotheses are defined. A justification of the sample size is provided in Section 7.5.

Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the study; i.e., confidence intervals are considered as interval estimates for effects.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The following analysis sets will be defined for this trial:

- Treated Set (TS):
  The Treated Set (TS) consists of patients who are randomised to a treatment group and receive at least one dose of study medication.
- Per Protocol Set (PPS):
  The Per Protocol Set (PPS) will consist of patients from TS considering exclusion from the set based on important protocol deviations.
- Pharmacokinetic Parameter Analysis Set (PKS):
  The Pharmacokinetic Parameter Analysis Set (PKS) includes all patients in the Treated Set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a patient will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment.

Descriptive and model based analyses of PK parameters will be based on the PKS. All other analyses will be based on the TS.

Pharmacokinetics:

The pharmacokinetic parameters listed in Section 2.1 and Section 2.2 for nintedanib will be calculated using Phoenix WinNonlinTM software (version 6.3 or higher, [redacted]) or SAS® Version 9.4 (or later version) by means of noncompartmental analysis and according to the relevant SOP of the sponsor.

Plasma concentration data and parameters of a subject will be included in the PK analyses, if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Blinded Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.
Patients who are considered as not evaluable will be listed with their individual plasma concentrations and individual pharmacokinetic parameters. However they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment apart from safety evaluation.

Plasma concentrations will be plotted graphically versus time for all patients as listed in the drug plasma concentration-time tables. Only concentrations within the validated concentration range and actual sampling-times will be used for the calculation of pharmacokinetic parameters. For the presentation of the mean profiles, the arithmetic mean and the planned blood sampling times will be used.

Handling and derivation of pharmacokinetic parameters will be done according to BI standards.

The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations (i.e. three significant digits). The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the integrated Quality and Risk Management Plan (IQRMP). IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

All analyses will be based on the actual treatment group. Details will be specified in the TSAP.

Patients without any post-randomization data will be handled as missing for the respective endpoints and assessments (see Section 7.3).

Handling of anticipated problems (e.g. planned data transformations based on the expected distributional characteristics or convergence of the mixed models) will be addressed in the TSAP.

7.2.2 Primary endpoint analyses

For the primary PK analysis, the area under the plasma concentration-time curve at steady state (AUCτ,ss) will be calculated by non-compartmental as well as compartmental analysis and descriptive statistics will be provided as detailed in Section 7.2.1.
For patients receiving nintedanib in Part A, PK profiles on week 2 and week 26 are planned to be collected. For the primary endpoint AUCτ,ss the AUCτ,ss at week 2 will be used. If the week 2 value is missing, then it will be replaced by available AUCτ,ss at week 26. For patients receiving placebo in Part A and nintedanib in Part B, AUCτ,ss evaluated based on PK profiles at week 26 will be used (which corresponds to week 2 on active treatment). Further details on the PK analysis will be specified in the TSAP.

The primary safety endpoint listed in Section 2.1.2 will be derived according to BI standards. For the primary analysis, only treatment emergent AEs during the double-blind period until week 24 will be included. The analysis will be based on the TS and will be descriptive in nature.

Subgroup analyses will be specified in the TSAP.

7.2.3 Secondary endpoint analyses

Analysis of secondary endpoints listed in Section 2.1.3 will be descriptive in nature using a mixed model with repeated measurements (MMRM) for continuous endpoints. Time-to-event endpoints will be displayed descriptively using the Kaplan-Meier method. Categorical endpoints, safety and tolerability will be displayed descriptively in frequency tables. Further details will be provided in the TSAP.

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 28 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

As this study consists of a double-blind, placebo-controlled part (Part A) and an open-label part (Part B), two treatment periods will be used for analysis and definition of 'treatment-emergent':

1. Double-blind period: Only adverse events assigned to the on-treatment period with onset during the double-blind period will be considered for the analysis.
2. Whole-trial period: All adverse events assigned to the on-treatment period will be considered for the analysis.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

[redacted]

7.2.7 Interim Analyses

No interim analysis is planned, but a SMC will be in place with tasks as described in Section 8.7.

Furthermore, the study will include two database locks (DBL 1 and DBL 2). The first DBL will be announced once 30 patients (at least 20 adolescents aged 12-17 years, and if feasible at least 10 children aged 6-11 years) have completed PK sampling at 26 weeks, or prematurely discontinued the trial (last-patient-last-visit-primary-endpoint). At this timepoint patient recruitment will close. Based on the data from DBL 1 (or updated DBL 1 data once the number of patients with sufficient PK data has been reached), the primary analysis and a benefit-risk assessment will be done and the clinical trial report for the primary analysis will

be written. If PK data collected for the primary analysis are not sufficient, then further PK data will be collected as explained in Section 3.1.
The timing of final DBL (DBL 2) and EoT visit will be communicated after confirming adequacy of PK data from DBL 1 (or updated DBL 1 data). Please see Section 3.1 for further details.

Moreover, the primary analysis may be conducted while the data collection for selected other analyses is still ongoing.

7.3 HANDLING OF MISSING DATA

In general, missing data will not be imputed.

Missing or incomplete AE onset and end dates are imputed according to BI standards.

The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption".
In the analysis of time-to-event endpoints, missing or incomplete data will be handled using standard survival analysis techniques (i.e. censoring).

In the analyses of the binary endpoints, multiple imputation will be used to handle missing data at week 24. For week 52 and later, data will not be imputed and only observed values will be used.

For pharmacokinetics:

Handling of missing PK data will be performed according to BI standards. For the non-compartmental analysis, concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed) will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ (below the limit of quantification), and NOP (no peak detectable) values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.4 RANDOMISATION

Patients will be randomised to each treatment group with an approximate ratio of 2:1 (nintedanib:placebo) stratified by age group (6 - <12 years; 12 - <18 years). BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

For the primary evaluation of PK including the assessment on whether nintedanib exposure at steady-state ($AUC_{\tau,ss}$) in paediatric patients is comparable to adult exposure, the clearance

parameter needs to be estimated with adequate precision. Assuming a coefficient of variation (CV) of 70.8% (based on geometric CV [gCV] of apparent clearance at steady-state [CL/Fss] after extravascular administration observed in the PK meta-analysis [U11-1639-01]), at least 20 actively treated patients with available PK measurements per age group (6 - <12 years; 12 - <18 years) would be needed to achieve at least 80% probability (loosely referred to as power in this context [R12-0884]) of having the 95% CI of nintedanib CL/F_{ss} and with this $AUC\tau,ss$ within 60% and 140% of the geometric mean estimate. This calculation was performed as described by Wang et al. [R12-0884] using R Version 3.5.1.

Table 7.5: 1 provides an overview of the achievable probability of having the 95% CI of nintedanib CL/F_{ss} and with this $AUC\tau,ss$ within 60% and 140% of the geometric mean estimate.

Table 7.5: 1 Probability that can be expected of having the 95% CI of nintedanib CL/F_{ss} and with this $AUC\tau,ss$ within 60% and 140% of the geometric mean estimate.

gCV [%]	Sample Size	Probability [%]
60	16	80.60
60	18	91.20
60	20	96.82
60	22	99.10
60	24	99.81
70.8	16	52.82
70.8	18	68.03
70.8	20	81.03
70.8	22	90.32
70.8	24	95.82
80	16	32.78
80	18	45.71
80	20	59.64
80	22	72.81
80	24	83.63

Based on the inclusion criteria of the proposed study and preliminary feasibility assessment, it is anticipated that the study will only be powered for patients with ≥12 years of age. PK parameters in children <12 years will be collected and analysed but are expected to be limited due to expected small number of patients falling in that age range.

To further optimise PK assessment from the study population, on-treatment PK sampling is planned in those assigned to placebo after switching to active treatment. By this, 30 randomized paediatric patients have the possibility to contribute for the PK assessment at the time of primary analysis. This increases the sample size for the PK analysis.

The target sample size of a minimum of 30 patients is based on the sample size estimation for the evaluation of the primary endpoint of PK and trial feasibility evaluation. Although the planned basket approach makes it feasible to evaluate this extremely rare patient population, one of the limitations of this approach is the heterogeneity of the study populations, especially in evaluating efficacy outcomes of potential interest (e.g. lung function). Due to the high unmet medical need, lack of therapeutic options and the potential for more robust efficacy evaluation, patient recruitment into the treatment phase will remain open until 30 patients (at least 20 adolescents aged 12-17 years, and if feasible at least 10 children aged 6-11 years) have completed PK sampling at 26 weeks, or prematurely discontinued the trial. This will allow for any eligible patient identified beyond the target (i.e. 30 subjects randomized including at least 20 adolescents aged 12-17 years) to have access to study drug. Although the duration of the blinded treatment period (Part A) will be variable in some of these patients, all PK and clinical data collected will be used in the primary analysis to allow for more robust estimate of exposure and potential treatment effect.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from the patient’s legally accepted representative (and written informed assent must be obtained from the patient, where applicable) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent (and assent where applicable) and any additional parental information form (and patient information form where applicable) retained by the investigator as part of the trial records. A signed copy of the informed consent (and assent where applicable) and any additional parental information (and patient information where applicable) must be given to the patient’s legally accepted representative (and the patient, where applicable).
The patient and the patient’s legally accepted representative must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient’s legally accepted representative own free will with the informed consent form after confirming that the representative understands the contents. Moreover, where applicable, the investigator or delegate obtains written assent of the patient’s own free will with the informed

assent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form (and the informed assent form where applicable). If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent (and the informed assent where applicable).
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process (together with the assent and re-assenting process where applicable) should be properly documented in the source documentation.
In order to ensure continued consent and assent, the investigator or [redacted] delegate will seek affirmation from the patient and patient's legally accepted representative as applicable about the continuation of the patient's participation in the trial during each visit. The fact that the patient appears for the regular visit as per protocol is enough affirmation in this aspect mean. The regular visit must be documented in the patient's medical records.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent (and assent where applicable) documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to

retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Data will be collected as follows:

- data recorded in patient's files and transcribed into the CRF
- data collected at site using materials/instruments provided by vendors, analysed/checked at vendors and transferred from vendors to the sponsor (e.g. safety analyses and pregnancy tests, PK analyses, spirometry)
- data captured electronically at site, transferred to vendors and from vendors to the sponsor (e.g. HRCT, bone MRI/x-ray assessments, panoramic x-rays)

Copies of source documents necessary for the purposes of the trial will be provided to the relevant committee/vendor, as listed below: to the Disease Review Committee for retrospective evaluation of patients' characteristics compared to protocol inclusion criteria, to the Adjudication Committee for the adjudication of defined events, to the Safety Monitoring Committee for the evaluation of possible efficacy signals and for monitoring of safety throughout the conduct of the study, to the external radiology expert for central reading of HRCTs, to the external pathology expert for central reading of biopsies, to the external radiology expert for central reading of bone MRIs/x-rays, to the external paediatric dentistry expert for central reading of panoramic x-rays. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.
If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For eCRF all data need to be derived from source documents, which need to be available on-site, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient and parent(s) / legal guardian were informed)
- Dates of patient's visits, including dispensing of trial medication and any dose change
- Dates of patient's contacts for the purpose of vital status
- Medical history (including trial indication and concomitant diseases)
- Medication history
- Adverse events (onset date mandatory, and end date if available*)
- Serious adverse events (onset date mandatory, and end date if available*)
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of

records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

* For adverse events, an end date may not always be available (e.g. due to hospital discharge and later recovery, or change in treating physician), but should be recorded in the source if known.

Source documents will include the following:

- physician's notes in patient files
- patient's / parent's / legal guardian's / site staff / physician's answers in worksheets (including PedsQL™ and 6MWT)
- laboratory print-outs
- biopsy slides including any reading by the pathology expert
- originals or copies of HRCT scans including any reading by the thoracic radiology expert
- originals or copies of bone MRI (or x-ray) scans including any reading by the radiology expert
- originals or copies of dental panoramic x-ray scans including any reading by the paediatric dentistry expert
- dentist's notes in patient files / dentist's answers in worksheets
- originals or copies of lung function test results
- originals or copies of D_{LCO} results
- original or copies of resting ECG

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents (and assents where applicable). The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1 The sponsor will also monitor compliance with the protocol and GCP.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, please see Section 6.1), site access may be restricted thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

- Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare.
- Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place

- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed assent (where applicable, and) has informed consent signed by parent(s) / legal guardian.
The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early**

termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority (HA) request.
The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within six months from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator chosen among experts in the field of paediatric ILD is responsible to provide expert medical support and coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

The targeted (Principal) Investigators will be paediatricians, pulmonologists, rheumatologists, and other physicians responsible for the investigational sites. Study sites will consist of specialized referral centres experienced in the management of ILDs in children. Relevant documentation on all participating (Principal) Investigators and other important study personnel, including their curricula vitae, will be filed in Investigator Site File (ISF).

A blinded external expert in thoracic radiology will review HRCT scans and confirm evidence of fibrosing ILD to the Investigator. Tasks and responsibilities are defined in a contract.

A blinded external pathology expert will review biopsies as needed and confirm evidence of fibrosing ILD to the Investigator. Tasks and responsibilities are defined in a contract.

A blinded external expert in radiology will review MRI/x-ray assessments of epiphyseal growth plates. Review by the external expert and images will be provided to the SMC for the evaluation of potential effects on bone development. Tasks and responsibilities are defined in a contract.

A blinded external expert in paediatric dentistry will review panoramic x-rays. Review by the external expert and images will be provided to the SMC for the evaluation of potential effects on teeth. Tasks and responsibilities are defined in a contract.

To determine how well the protocol inclusion criteria were able to identify the intended population, an independent Disease Review Committee (DRC) will be established to retrospectively review patient’s clinical data and results of HRCT and biopsy central reading

for all patients evaluated for study participation at Visit 1. Members of the committee will be blinded to patient screening outcome as well as patient treatment allocation. The composition of the DRC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the DRC members and the sponsor and also summarised in a DRC charter. Charter and meeting minutes will be filed in the TMF. The data will be collected at set interval and analysed after DBL 1.

A SMC composed of external experts independent from the trial and selected BI non-trial team members will be established to review individual and aggregated PK and safety data at regular intervals to determine the safety profile and risk/benefit ratio and recommend dose modification, additional assessments (e.g. laboratory tests), appropriateness of further enrolment and continuation/modification/premature interruption of the study. The SMC will also conduct regular reviews of the trial safety data, including MRI/x-rays assessments, height measurements, and panoramic x-rays, as detailed in Section 3.1, in Section 5.2.5. Details of the SMC responsibilities and procedures are described in the SMC charter.

An independent Adjudication Committee (AC) will review all fatal cases and adjudicate all deaths to either cardiac, respiratory or other causes, and review all adverse events categorized as MACE (see Section 5.2.7.2.4 for details).

A Steering Committee will provide scientific advice on the clinical development program of nintedanib in the paediatric population. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs. Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service, a central spirometry service, central imaging services and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory / Spirometry / Imaging Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P04-08733 The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004. 114 (2, Part 3) (Suppl): 555-576.

P05-12782 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005. 26 (2): 319-338.

P06-05020 King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am. J Respir Crit Care Med. 2001. 164(17): 1171-1181.

P08-08684 Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008. 68 (12): 4774-4782.

P11-07084 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An officialATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011. 183(6): 788-824.

P12-09611 du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011. 184(12): 1382-1389.

P14-02860 Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B, Anti-fibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor, nintedanib, in experimental models of lung fibrosis. J Pharmacol Exp Ther. 2014. 349: 209-220.

P14-07514 Richeldi L, et al, INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England Journal of Medicine, published on May 18, 2014, doi: 10.1056/NEJMoa1402584. N Engl J Med. 2014. 370(22): 2071-2082.

P14-07999 Wollin L, Ostermann A, Wex E, Herrmann FE, Doods H. Nintedanib attenuates motility of lung fibroblasts from patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014. 189, A2008, Abstr.

P14-17410 Hostettler KE, Zhong J, Papakonstantinou E, Karakiulakis G, Tamm M, Seidel P, Sun Q, Mandal J, Lardinois D, Lambers C, Roth M Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. Respir Res (Lond). 2014. 15, 157.

P15-06100 Huang J, Beyer C, Palumbo-Zerr K, Zhang Y, Ramming A, Distler A, Gelse K, Distler O, Schett G, Wollin L, Distler JHW. Nintedanib inhibits fibroblast activation and ameliorates fibrosis in preclinical models of systemic sclerosis. Ann Rheum Dis. 2016. 75 (5): 883-890.

P16-01479 Hyldgaard C, Hilberg O, Muller A, Bendstrup E. A cohort study of interstitial lung diseases in central Denmark. Respir Med. 2014. 108(5): 793-799.

P16-05905 Wollin L, Schuett J, Ostermann A, Herrmann F. The effect of nintedanib on platelet derived growth factor-stimulated contraction of human primary lung fibroblasts. Am J Respir Crit Care Med. 2016. 193, A2384, Abstr.

P17-03310 Ackermann M, Kim YO, Wagner WL, Schuppan D, Valenzuela CD, Mentzer SJ, et al. Effects of nintedanib on the microvascular architecture in a lung fibrosis model. Angiogenesis. 2017. 20 (3): 359-372.

P17-06049 Tandon K, Herrmann F, Ayaub E, Parthasarathy P, Ackermann M, Inman MD, et al. Nintedanib attenuates the polarization of profibrotic macrophages through the inhibition of tyrosine phosphorylation on CSF1 receptor. Am J Respir Crit Care Med. 2017. 195, A2397, Abstr.

P17-06052 Wollin L, Ostermann A, Brauchle V, Williams C. Nintedanib inhibits pro-fibrotic mediators with relevance in connective tissue disease-associated interstitial lung diseases. ATS 2017, 113th Int Conf of the American Thoracic Society (ATS), Washington, 19 - 24 May 2017. Am J Respir Crit Care Med. 2017. 195, A2450, Abstr.

P17-07763 Distler O, Brown KK, Distler JHW, Assassi S, Maher TM, Cottin V, et al, SENSCIS Trial Investigators. Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS). Clin Exp Rheumatol. 2017. 35(4) (Suppl 106): S75-S81.

P17-10564 Huang J, Maier C, Zhang Y, Soare A, Dees C, Beyer C, et al. Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the Fra2 mouse model of systemic sclerosis. Ann Rheum Dis. 2017. 76 (11): 1941-1948.

P17-10582 Flaherty KR, Brown KR, Wells AU, Clerisme-Beaty E, Collard HR, Cottin V, et al. Design of the PF-ILD trial: a doubleblind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Resp Res. 2017. 4: e000212.

P18-00197 Hilberg F, Tontsch-Grunt U, Baum A, Le AT, Doebele RC, Lieb S, et al. The triple angiokinase inhibitor nintedanib directly inhibits tumor cell growth and induces tumor shrinkage via blocking oncogenic receptor tyrosine kinases. J Pharmacol Exp Ther. 2018- 364(3): 494-503.

P18-02512 Redente EF, Aguilar MA, Black BP, Edelman BL, Bahadur AN, Humphries SM, et al. Nintedanib reduces pulmonary fibrosis in a model of rheumatoid arthritis-associated interstitial lung disease. Am J Physiol. 2018. 314 (6), L998 - L1009.

P18-05607 Akter T, Atanelishvili I, Noguchi A, Wollin L, Silver RM, Bogatkevich GS. Molecular evidences for antifibrotic potential of nintedanib in

interstitial lung disease associated with systemic sclerosis. Am J Respir Crit Care Med. 2018. 197, A4638, Abstr.

P18-05618 Prasse A, Plappert L, Jaeger B, Wollin L. Nintedanib treatment attenuates pulmonary fibrosis in a new humanized mouse model for IPF. ATS 2018, 114th Int Conf of the American Thoracic Society (ATS), San Diego, 18 - 23 May 2018. Am J Respir Crit Care Med. 2018. 197, A5754, Abstr.

P18-08230 Kidokoro K, Sogawa Y, Cherney D, Kulasingam V, Nagasu H, Satoh M, et al. Evaluation of glomerular hemodynamic function by empagliflozin in diabetic mice using in vivo imaging. 78th Sci Sess of the American Diabetes Association (ADA), Orlando, 22 - 26 Jun 2018. Diabetes. 2018. 67 (Suppl 1), A23, Abstr 89-OR.

P19-02553 Deterding RR. Children's interstitial and diffuse lung disease. Progress and future horizons. Ann Am Thorac Soc. 2015. 12: 1451-1457.

P19-04387 Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al, SENSCIS Trial Investigators. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med. 2019.

P19-08802 Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al, INBUILD Trial Investigators. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. NEJM. Published Online September 29, 2019, doi: 10.1056/NEJMoa1908681; 2019.

P20-02333 Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al, INBUILD Trial Investigators. Nintedanib in patients with progressive fibrosing interstitial lung diseases - subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respiratory Medicine, Published Online March 5, 2020, doi: 10.1016/S2213-2600(20)30036-9; 2020.

R03-2075 Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med. 1994. 150(4): 967-972.

R03-2090 Thomeer M, Demedts M, Vandeurzen K, VRGT Working Group on Interstitial Lung Diseases. Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders. Acta Clin Belg. 2001. 56(3): 163-172.

R06-2002 Macintyre N, Crapo RO, Viegi G, Johnson DC, Grinten CPM van der, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005. 26(4): 720-735.

R06-4127 Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003. 168(5): 538-542.

R06-4129 Jegal Y, Kim DS, Shim TS, Lim CM, Do Lee S, Koh Y, et al. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. Am J Respir Crit Care Med. 2005. 171(6): 639-644.

R09-5337 Fan LL, Kozinetz CA. Factors influencing survival in children with chronic interstitial lung disease. Am J Respir Crit Care Med. 1997. 156: 939–942.

R10-0828 Schwartz GJ, Brion LP, Spitzer A The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987. 34(3): 571-590.

R10-2727 Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur Respir J. 2010. 35(4): 830-836.

R10-6539 Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, Travis WD, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003. 168(5): 543-548.

R11-4789 Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009. 20: 629-637.

R11-5060 Karakatsani A, Papkosta D, Rapti A, Antoniou KM, Dimadi M, Markolpolou A, et al. Epidemiology of interstitial lung diseases in Greece. Respir Med. 2009. 103(8): 1122-1129.

R12-0299 Dobias L, Cerna M, Rossner P, Sram R. Genotoxicity and carcinogenicity of metronidazole. Mutat Res Rev Genet Toxicol. 1994. 317: 177-194.

R12-0358 Xaubet A, Ancochea J, Morell F, Rodriguez-Arias JM, Villena V, Blanquer R, et al. Report on the incidence of interstitial lung diseases in Spain. Sarcoidosis Vasc Diffuse Lung Dis. 2004. 21(1): 64-70.

R12-0884 Wang Y, Jadhav PR, Lala M, Gobburu JV Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J Clin Pharmacol. 2012. 52: 1601-1606.

R12-0974 López-Campos JL, Rodríguez-Becerra E, Neumosur Task Group, Registry of Interstitial Lung Diseases. Incidence of interstitial lung diseases in the south of Spain 1998-2000: the RENIA study. Eur J Epidemiol. 2004. 19(2): 155-161.

R12-2794 Dinwiddie R, Sharief N, Crawford O. Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. Pediatr Pulmonol. 2002. 34(1): 23-29.

R12-3648 Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, et al. Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. Thorax. 2012. 67(5): 407-411.

R14-1149 Schmidt SL, Nambiar AM, Tayob N, Sundaram B, Han MK, Gross BH, et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. Eur Respir J. 2011. 38(1): 176-183.

R14-1150 Schmidt SL, Tayob N, Han MK, Zappala C, Kervitsky D, Murray S, et al. Predicting pulmonary fibrosis disease course from past trends in pulmonary function. Chest. 2014. 145(3): 579-585.

R14-4379 Musellim B, Okumus G, Uzaslan E, Akgün M, Cetinkaya E, Turan O, et al. Epidemiology and distribution of interstitial lung diseases in Turkey. Clin Respir J. 2014. 8(1): 55-62.

R15-0845 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. on behalf of the ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3 - 95 year age range: the global lung function 2012 equations: report of the Global Lung Function Initiative (GLI), ERS task force to establish improved lung function reference values. Eur Respir J. 2012. 40(6): 1324-1343.

R16-0560 Lynch DA, Godwin JD, Safrin S, Starko KM, Hormel P, Brown KK, et al. Highresolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med. 2005. 172(4): 488-493.

R16-0752 Edey AJ, Devaraj AA, Barker RP, Nicholson AG, Wells AU, Hansell DM. Fibrotic idiopathic interstitial pneumonias: HRCT findings that predict mortality. Eur Radiol. 2011. 21(8): 1586-1593.

R16-0754 Han MK, Murray S, Fell CD, Flaherty KR, Toews GB, Myers J, et al. Sex differences in physiological progression of idiopathic pulmonary fibrosis. Eur Respir J. 2008. 31(6): 1183-1188.

R16-0755 Lee SH, Shim HS, Cho SH, Kim SY, Lee SK, Son JY, et al. Prognostic factors for idiopathic pulmonary fibrosis: clinical, physiologic, pathologic and molecular aspects. Sarcoidosis Vasc Diffuse Lung Dis. 2011. 28(2): 102-112.

R16-0756 Mogulkoc N, Brutsche MH, Bishop PW, Greaves SM, Horrocks AW, Egan JJ, et al. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. Am J Respir Crit Care Med. 2001. 164(1): 103-108.

R16-0758 Shin KM, Lee KS, Chung MP, Han J, Bae YA, Kim TS, et al. Prognostic determinants among clinical, thin-section CT and histopathologic findings for fibrotic idiopathic interstitial pneumonias: tertiary hospital study. Radiology. 2008. 249(1): 328-337.

R16-1141 Griese M, Haug M, Brasch F, Freihorst A, Lohse P,von Kries R, et al. Incidence and classification of pediatric diffuse parenchymal lung diseases in Germany. Orphanet J Rare Dis. 2009. 4:26.

R16-4788 Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med. 2013. 188(3): 376-374.

R16-4790 Casamento K, Laverty A, Wilsher M, Twiss J, Gabbay E, Glaspole I, et al. Assessing the feasibility of a web-based registry for multiple orphan lung diseases: the Australasian Registry Network for Orphan Lung Disease (ARNOLD) experience. Orphanet J Rare Dis. 2016. 11: 42.

R17-1625 Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al Short term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol. 2017. 69(8): 1670-1678.

R17-2776 Saddi V, Beggs S, Bennetts B, Harrison J, Hime N, Kapur N, et al. Childhood interstitial lung diseases in immunocompetent children in Australia and New Zealand: a decade's experience. Orphanet J Rare Dis. 2017. 12: 133.

R17-2810 Duchemann B et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J. 2017. 50(2). Pii:1602419.

R17-2902 Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, Sanyal S, Brillet PY, Brauner M, et al. Interstitial lung disease in Malta. Malta Medical Journal. 2012. 24(2): 11-15.

R17-2907 Annesi-Maesano I, Nunes H, Duchemann B, Valeyre D, Agabiti N, Saltini C, et al. Epidemiology of idiopathic pulmonary fibrosis in Europe - an update. Sarcoidosis Vasc Diffuse Lung Dis. 2013. 30(Suppl 1): 6-12.

R17-3628 Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014. 44: 1428-1446.

R18-1147 Laverty A, Jaffé A, Cunningham S. Establishment of a web-based registry for rare (orphan) pediatric lung diseases in the United Kingdom: the BPOLD registry. Pediatr Pulmonol. 2008. 43(5): 451-456.

R18-1357 U.S. Department of Health and Human Services Common terminology criteria for adverse events (CTCAE) version 5.0 (published: November 27, 2017). U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. 2017.

R18-1476 Voss SD, Glade-Bender J, Spunt SL, DuBois SG, Widemann BC, Park JR, et al. Growth plate abnormalities in pediatric cancer patients undergoing phase 1 antiangiogenic therapy: a report from the children's oncology group phase I consortium. Pediatr Blood Cancer. 2015. 62(1): 45-51.

R18-1477 Kim A, Dombi E, Solomon J, Fox E, Balis FM, Widemann BC. Automated volumetric growth plate measurement using magnetic

resonance imaging for monitoring skeletal toxicity in children treated on investigational drug trials. Clin Cancer Res. 2011. 17(18): 5982-5990.

R18-3409 Sobanski V, Vries-Bouwstra J de, Hoffmann-Vold AM, Huscher D, Alves M, Matucci-Cerinic M, et al, EUSTAR Association of short-term longitudinal changes in clinical and physiologic variables with overall survival in patients with systemic sclerosis-associated interstitial lung disease. ACR/ARHP Sci Mtg 2018, 82nd Ann Mtg of the American College of Rheumatology and 53rd Ann Mtg of the Association of Rheumatology Health Professionals, Chicago, 19 - 24 Oct 2018 (Poster)

R18-3555 Volkmann ER, Tashkin DP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L, et al. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. Ann Rheum Dis. 2018.

R19-0760 Niemitz M, Schwerk N, Goldbeck L, Griese M. Development and validation of a health-related quality of life questionnaire for pediatric patients with interstitial lung disease. Pediatr Pulmonol. 2018. 53: 954-963.

R18-2970 Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progessive fibrosing interstitial lung disease: design of a double-blind, randomised, placebo-controlled phase II trial. BMJ Open Respir Res 5, e000289 (2018).

R19-0805 Griese M. Chronic interstitial lung disease in children. EurRespirRev. 2018. 27 (147), 170100.

9.2 UNPUBLISHED REFERENCES

U07-1710 [redacted] Internal report. 07B002. 28 August 2007.

U07-1814 [redacted] Internal report. 07B030. 21 January 2008.

U10-1991 [redacted] Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy (LUME Lung 1). Trial 1199.13. 19 Sep 2012.

U11-1639-01 [redacted] Metaanalysis of noncompartmental pharmacokinetic parameters, influence of covariates, and exploratory PK/AE investigations across BIBF 1120 monotherapy Phase I studies in oncology patients. Study numbers 1199.1, 1199_PK Metaa. Cancer Pat. Mono.,1199.19, 1199.3, 1199.2. 10 June 2011.

U13-1478-01 [redacted] Relative bioavailability of a single oral dose of nintedanib given alone and in

combination with multiple oral doses of rifampicin in healthy male volunteers (an open-label, two-period, fixed-sequence clinical Phase I trial). Study 1199.162. 8 August 2013.

U13-1504 [redacted] Multicentre, randomised, double-blind, Phase III trial to investigatze the efficay and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy (LUME Lung 1). Clinical Reports 1199.13. 26 August 2013.

U13-1506 Clinical Overview: Nintedanib (BIBF 1120) soft capsules, 150 mg, 100 mg. 02 Sep 2013.

U13-1925 [redacted]Relative bioavailability of nintedanib given alone and in combination with ketoconazole at steady state in healthy male volunteers (an open-label, randomised, two-way cross-over clinical Phase I study). Study 1199.161. 4 July 2013.

c02153150 Clinical Overview: Nintedanib (BIBF 1120) soft capsules, 150 mg 100 mg. 07 April 2014.

c01783972-16 Investigator's Brochure Nintedanib (BIBF 1120), Indications: Idiopathic Pulmonary Fibrosis, Systemic Sclerosis, Progressive Fibrosing Interstitial Lung Disease. Version 18, 16 December 2020.

10. APPENDICES

10.1 FAN SEVERITY SCORE

The severity-of-illness score assigned by the investigator at Visit 2 will be based on information in the patient records at the time of initial evaluation [R09-5337]. Refer to Table 10.1: 1 for details.

Table 10.1: 1 Severity-of-illness score

SEVERITY-OF-ILLNESS SCORE
1. Asymptomatic
2. Symptomatic, normal room air oxygen saturation under all conditions
3. Symptomatic, normal resting room air saturation, but abnormal saturation (< 90%) with sleep or exercise
4. Symptomatic, abnormal resting room air saturation (< 90%)
5. Symptomatic with pulmonary hypertension

10.2 CREATININE CLEARANCE

Calculation of creatinine clearance according to Schwartz Formula [R10-0828]

Conventional:

- in adolescent males k=0.70:
  GFR (mL/min./1.73m^2) = height (cm) x 0.70 / serum creatinine (mg/dL)

- in adolescent females k=0.55:
  GFR (mL/min./1.73m^2) = height (cm) x 0.55 / serum creatinine (mg/dL)

SI:

- in adolescent males k=0.70:
  GFR (mL/min./1.73m^2) = height (cm) x 0.70 / (serum creatinine (µmol/L) x 0.01131)

- in adolescent females k=0.55:
  GFR (mL/min./1.73m^2) = height (cm) x 0.55 / (serum creatinine (µmol/L) x 0.01131)

Calculation of creatinine clearance according to Schwartz Formula [R11-4789]

Conventional:

- in children 2-12 years of age k=0.41:
  GFR (mL/min/1.73m^2) = height (cm) x 0.41 / serum creatinine (mg/dL)

SI:

- in children 2-12 years of age k=0.41:
  GFR (mL/min/1.73m^2) = height (cm) x 0.41 / (serum creatinine (µmol/L) x 0.01131)

10.3 EQUATIONS FOR D_{LCO} ADJUSTMENT FOR HAEMOGLOBIN

Percent predicted D_{LCO} results from Visit 2 will be corrected for haemoglobin (value obtained at Visit 1) by the site.

Percent predicted D_{LCO} corrected for haemoglobin (Hb) expressed in $g \cdot dL^{-1}$ [R06-2002] can be calculated as follows:

- In adolescents (and adult males)
  D_{LCO} predicted corrected for Hb = D_{LCO} predicted x (1.7Hb)/(10.22+Hb)

- In children <15 years of age and females
  D_{LCO} predicted corrected for Hb = D_{LCO} predicted x (1.7Hb)/(9.38+Hb)

10.4 RECOMMENDATIONS FOR AMBULATORY (OFFICE) BLOOD PRESSURE MEASUREMENTS IN CHILDREN AND ADOLESCENTS

Recommendations for ambulatory (office) blood pressure measurements in children and adolescents [P04-08733]:

- The recommended method is auscultation
- Use K1 for systolic BP and K5 for diastolic BP
- If the oscillometric method is used, the monitor needs to be validated
- All abnormal values by oscillometric method need confirmation by auscultation
- Use the appropriate cuff size according to arm width

Table 10.4: 1 Recommended Dimensions for BP Cuff Bladders

Age Range	Width, cm	Length, cm	Maximum Arm Circumference, cm*
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small adult	10	24	26
Adult	13	30	34
Large adult	16	38	44
Thigh	20	42	52

* Calculated so that the largest arm would still allow the bladder to encircle arm by at least 80%.

Predicted Equations for Blood Pressure Levels

NOTE: The predicted equations are being provided as an appendix for documentation purposes; they are not intended for use by individual sites.

Table 10.4: 2 Predicted equations for Blood Pressure: white boys aged 1-10 years (from [P04-08733])

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Table 10.4: 3 Predicted equations for Blood Pressure: white boys aged 11-17 years (from [P04-08733])

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Table 10.4: 4 Predicted equations for Blood Pressure: white girls aged 1- 10 years (from [P04-08733])

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Table 10.4: 5 Predicted equations for Blood Pressure: white girls aged 11- 17 years (from [P04-08733])

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

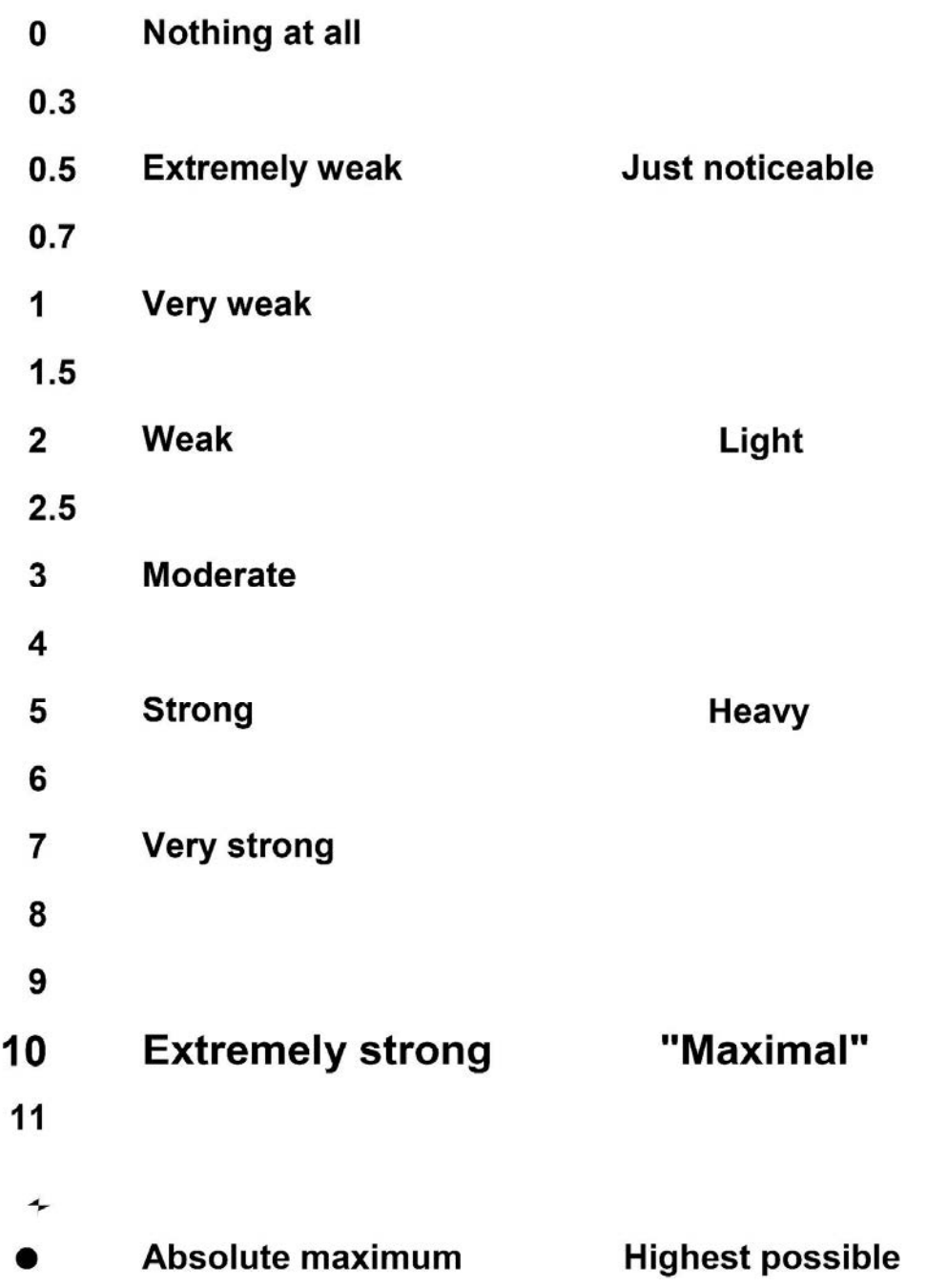
For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

10.5 SIX-MINUTE WALK TEST

The methodology of the six-minute walk test is based on the ATS/ERS Technical Standards on the 6-minute walk test [R17-3628]. Instructions will be provided in the ISF.

10.6 BORG CR-10 SCALE

Instructions will be provided in the ISF.



10.7 PEDSQL

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YOUNG CHILD REPORT (ages **5-7**)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL 2

Think about how you have been doing for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING *(problems with...)*	Not at all	Some-times	A lot
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have hurts or aches (*Where?*_____)	0	2	4
8. Do you ever feel too tired to play	0	2	4

Remember, tell me how much of a problem this has been for you for the last few weeks.

EMOTIONAL FUNCTIONING *(problems with...)*	Not at all	Some-times	A lot
1. Do you feel scared	0	2	4
2. Do you feel sad	0	2	4
3. Do you feel mad	0	2	4
4. Do you have trouble sleeping	0	2	4
5. Do you worry about what will happen to you	0	2	4

SOCIAL FUNCTIONING *(problems with...)*	Not at all	Some-times	A lot
1. Is it hard for you to get along with other kids	0	2	4
2. Do other kids say they do not want to play with you	0	2	4
3. Do other kids tease you	0	2	4
4. Can other kids do things that you cannot do	0	2	4
5. Is it hard for you to keep up when you play with other kids	0	2	4

SCHOOL FUNCTIONING *(problems with...)*	Not at all	Some-times	A lot
1. Is it hard for you to pay attention in school	0	2	4
2. Do you forget things	0	2	4
3. Is it hard to keep up with schoolwork	0	2	4
4. Do you miss school because of not feeling good	0	2	4
5. Do you miss school because you have to go to the doctor's or hospital	0	2	4

How much of a problem is this for you?

Not at all

Sometimes

A lot

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PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

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CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

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PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

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TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

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PARENT REPORT for **TEENS** (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

PedsQL™ Administration Guidelines℠

The following guidelines are intended for use by individuals trained in the administration of standardized questionnaires. The PedsQL™ administrator is crucial in developing rapport with the respondents, emphasizing the importance of the questionnaire, addressing concerns, and ensuring that the PedsQL™ is completed accurately and confidentially.

General Protocol

1. Create a procedure for assigning identification numbers that will allow for parent/child comparisons as well as comparisons of baseline/follow-up data.
2. If feasible, the PedsQL™ should be completed *before* the respondents complete any other health data forms and *before* they see their physician or healthcare provider.
3. The parent/child should first complete the PedsQL™ Generic Core Scales and then complete any additional PedsQL™ Module.
4. Parents, Children (8-12) and Teens (13-18) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen. For the Young Child (5-7), the PedsQL™ should be administered by reading the instructions and each item to the young child word for word. At the beginning of each subscale repeat the recall interval instructions (one month or 7 days) to remind the young child to respond only for that specific recall interval. Use the separate page with the three faces response choices to help the young child understand how to answer. When reading items aloud to a child, intonation should be kept neutral to avoid suggesting an answer.
5. If a child has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the child (e.g., administering the Young Child (5-7) Self-Report version with the three faces response choices to an 8 year old). However, if a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL™ may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent.
6. The parent and child must complete the questionnaires *independently* of one another. Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires, but that it is important to get both the parent's and the child's *individual* perspectives. If you are administering the questionnaire to the child, the child should be facing away from the parent.
7. If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what *they think the question means*. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child and/or the parent has the option of not answering a question if they truly do not understand the question.
8. If a parent/child asks you to interpret the responses, tell her/him that you are not trained to interpret or provide a score for the answers given. If the PedsQL™ is being used for a

clinical study, let the parent/child know that their answers will be combined with other participants' answers and analysed as a group rather than as individual respondents.

9. Document all reasons for refusals and non-completions of the PedsQL™.

Administering the PedsQL™

1. The following scripts have been developed as a guide to introduce the PedsQL™ to the child and his/her parent(s). Modify the language to a style that is most appropriate for you and the respondent.

   For the child:

   The PedsQL™ asks you questions about how you feel and what you think about your health. It is not a test, and there are no right or wrong answers. It takes about 5 minutes to complete. If you have any questions, please let me know.

   For the parent:

   The PedsQL™ is a questionnaire that assesses health-related quality of life in children and adolescents. It contains questions about your child's physical, emotional, social, and school functioning ***in the past one month (****or for the Acute version****, in the past 7 days)****.*

   The PedsQL™ is brief and typically takes less than 5 minutes to complete. It is not a test, and there are no right or wrong answers. Please be sure to read the instructions carefully and choose the response that is the closest to how you truly feel. Please do not compare your answers with your child's responses. We are interested in your and your child's ***individual*** *perspectives. However, feel free to discuss the questionnaire with your child* ***after*** *you have both completed it and returned it to me. If you have any questions, please let me know.*

2. Provide the respondent with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. Remain nearby should questions or concerns arise.
3. When the parent/child returns the PedsQL™, look it over and check to see that all answers have been completed. Verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, please ask the parent or child to indicate their response.
4. Ask the participants if they had any difficulties completing the questionnaire or if they have any other comments regarding the questionnaire. Document any important feedback.
5. Thank the parent and child for taking the time to complete the questionnaire. If the study design involves following up with these respondents, let them know that they may be asked to complete the PedsQL™ again at another time. Indicate when they can expect to be contacted again if known.

10.8 ACCEPTABILITY QUESTIONNAIRES

The assessment of acceptability of the investigational product based on the size and number of capsules will be performed by the patient using the acceptability questionnaire for the patient. If the patient is considered not old enough per investigator judgment, the parent/caregiver can assist with completion of the questionnaire.

Section to be completed before administration of the questionnaire

PATIENT NO.: ……
DATE OF COMPLETION: DD-MMM-YYYY
SIZE OF CAPSULES TAKEN DAILY: ☐ 150 MG, OR ☐ 100 MG, OR ☐ 25 MG

For 25 MG capsules ONLY
NUMBER OF CAPSULES TAKEN: IN THE MORNING _____
NUMBER OF CAPSULES TAKEN: IN THE EVENING _____

Acceptability questionnaire for the patient

We would like to learn about your impression of the study capsules.
Please take some time to answer the following questions.

For each question, please choose only the best applicable response.

QUESTION 1: HOW DOES IT FEEL WHEN YOU TAKE CAPSULES?

Very bad Bad Ok Good Very good

QUESTION 2: WAS TAKING THE STUDY CAPSULES (CHOOSE ONE OPTION):

- ☐ Very easy
- ☐ Easy
- ☐ Neither easy nor difficult
- ☐ Somewhat difficult
- ☐ Very difficult

QUESTION 3: HOW IS THE SIZE OF THE CAPSULE?

- ☐ OK (= acceptable)
- ☐ Large
- ☐ Very large

QUESTION 4: HOW EASY WAS TO SWALLOW THE GIVEN NUMBER OF CAPSULES? (CAPSULES SHOULD BE TAKEN WITH A GLASS OF WATER)

- ☐ I had no problem swallowing them (= acceptable)
- ☐ I swallowed them, but it was difficult
- ☐ I couldn't swallow them sometimes

QUESTION 5: COULD YOU TAKE THIS MEDICATION FOR A LONGER TIME PERIOD?

- ☐ yes
- ☐ no

Treatment acceptability questionnaire for the investigator or investigational site staff

Instructions:
For each question, please choose the response that most closely corresponds to this patient at the given time-point. Please consult the patient and his/her parents/caregiver if needed to answer the following questions:

QUESTION 1: WHAT IS YOUR IMPRESSION ABOUT THE PATIENT'S ACCEPTABILITY OF STUDY MEDICATION INTAKE? (CHOOSE ONE OPTION)

- ☐ Good
- ☐ Satisfactory
- ☐ Mediocre
- ☐ Bad
- ☐ Not assessable

QUESTION 2: STUDY MEDICATION INTAKE WAS POSSIBLE (CHOOSE ONE OPTION):

- ☐ Possible all the time
- ☐ Very often possible
- ☐ Occasionally not possible
- ☐ Often not possible
- ☐ Not assessable

QUESTION 3: IF THE DRUG WAS NOT TAKEN, WAS THIS DUE TO:
(CHECK ALL ANSWERS THAT YOU CONSIDER APPLICABLE FOR THIS PATIENT AT THIS POINT IN TIME)

- ☐ Lack of general well-being
- ☐ Difficulties to swallow the medication because of the capsule size
- ☐ Have forgotten the intake
- ☐ Other

Please specify _____

10.9 VISIT MODIFICATION IN EXCEPTIONAL CIRCUMSTANCES

In the event of force majeure or other disruptive circumstances (e.g. pandemic), in case site visits are temporarily not possible for individual patients, to ensure trial continuity the following measures may be implemented at a site if possible per local requirements in the participating country. Implemented measures should be documented and needed approvals should be obtained upon (see Section 6.1 and ISF for details).

Table 10.9: 1 Modifications to visit standard procedures in exceptional circumstances

STANDARD PROCEDURE	POSSIBLE MODIFICATION
Face-to-face patient visit performed by an adequate site staff under the responsibility of a physician on site.	• for Visit 3 Visit 4 and Visit 5: **no possibility to postpone the visits more than initial time window defined by CTP except in case of agreement with sponsor and after discussion and evaluation of individual patient benefit risk.** • for the following visits, visits may be converted to home visits, or combined home and remote visits. **If physical exam, vital signs, height, weight cannot be conducted at least every 16 weeks, the individual patient treatment needs to be interrupted upon discussion with the sponsor.** Medical decision has to be documented in patient's source notes. **Home visit** performed (with portable stadiometer, tape, scale, ECG machine, pulsoximeter to measure SpO_2) by the (sub)investigator or delegated and trained personnel to complete at least: • Physical examination and vital signs • Height sitting and standing • Leg length • Weight • ECG • SpO_2 • Safety Lab using central lab kits if possible (otherwise use local lab facility, see below for instructions) • Questionnaires administered as an interview using printed questionnaires (if not done by separate call, see below for instructions) • Transfer imaging CDs of bone MRI/x-ray and panoramic x-ray to site (when needed) • Collect medication for IMP compliance • Assessments listed under "Investigator Call," if not done by separate call **Investigator Call:** the following assessments could be completed by the (sub)investigator via phone or telemedicine, if not done during the home visit:

STANDARD PROCEDURE	POSSIBLE MODIFICATION
	[redacted] • ILD exacerbations • Hospitalizations • AEs, SAEs, AESI • Trial medication and concomitant medications • Questionnaires administered as an interview using printed questionnaires • Pregnancy status and pregnancy diary completion check The following assessments cannot be made outside the investigational site: • FVC • 6MWT • PK sampling [redacted] PK sampling will be conducted at the next scheduled visit at the site, as far as the study medication was regularly taken in the 10 days before PK sampling, and intake in the 3 days before PK sampling was documented in the PK diary card. FVC, 6MWT and [redacted] will be missed if the scheduled visit is converted to home visit, or combined home and remote visit.
Safety lab testing conducted at site using central lab kits • Haematology • Biochemistry • Electrolytes • Coagulation • Urinalysis •	Under treatment with nintedanib, regular safety lab including liver enzyme monitoring is required and needs to be ensured by the investigational site. If blood and urine sampling for safety lab testing at the trial site is not possible • samples could be collected at a local lab / local doctor using central lab kits and sent to central lab for analyses. If this is not possible, • safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and documents any clinically relevant safety issue as an adverse event. Safety lab tests including **liver function tests** should be conducted at the planned timepoint defined by CTP. **If safety lab tests cannot be conducted at least every 16 weeks, the individual patient treatment needs to be interrupted upon discussion with the sponsor.** Medical decision has to be documented in patient's source notes.
Pregnancy test on blood conducted at site using central lab kits – female subjects only	If blood sampling for pregnancy test at the trial site is not possible • Urine dipstick pregnancy tests will be used • Testing must occur every 4-6 weeks and results documented in the pregnancy test diary card. • The results of the pregnancy tests must be transferred to the investigator who ensures medical review, documents any test results as needed, and reports any positive results as defined by CTP.

STANDARD PROCEDURE	POSSIBLE MODIFICATION
	If pregnancy tests cannot be conducted every 4-6 weeks, the individual patient treatment needs to be interrupted upon discussion with the sponsor. Medical decision has to be documented in patient's source notes.
Follow-up monitoring of bone and teeth conducted at site/external facilities • Bone MRI/x-ray • Dental examination • Dental panoramic x-ray	If regular follow-up monitoring of bone and teeth at site is not possible • Bone MRI/x-ray, dental examination and dental panoramic x-ray can be performed at a local radiologist/ local dentist • The results (images and dental examination report) must be transferred to the investigator, who will send images to central reading, ensure medical review, and document any clinically relevant safety issue as an adverse event. Follow-up monitoring of bone and teeth should be conducted at the planned timepoint defined by CTP. **If bone MRI/x-ray and/or dental examination cannot be conducted at least every 16 weeks (first year)/28 weeks (second year), and/or if dental panoramic x-ray cannot be conducted at least every 28 weeks (first year)/1 year (thereafter), the individual patient treatment needs to be interrupted upon discussion with the sponsor.** Medical decision has to be documented in patient's source notes.
Dispensation of study medication on site	If study medication cannot be dispensed during a regular visit at the site • Direct to patient IMP shipment from Site can be requested • The patient's parent(s)/legal guardian (or the patient if applicable) must consent to provide contact details for shipping purposes • The patient's parent(s)/legal guardian (or the patient if applicable) should retain all unused IMP and packaging, and return it to the site as soon as possible (e.g. via Investigator in case of home visit, or when they are able to attend a visit at the site, or by other means defined with the site staff and approved by the sponsor).

The investigator will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the trial. The sponsor, where required, will support the investigator in their decision making. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the patient.

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		19 Jun 2020
EudraCT number **EU number**		2018-004530-14
BI Trial number		1199-0337 (InPedILD™)
BI Investigational Medicinal Product(s)		Ofev®, nintedanib
Title of protocol		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
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		4.1.5.1 Blinding
Description of change		"non-trial" added before "personnel from the sponsor involved in the PK analyses will be unblinded"; "after the 30th patient (either nintedanib or placebo) has completed planned PK assessment in Part A" removed at the end of the statement "In order to enable early analysis of PK, selected non-trial personnel from the sponsor involved in the PK analyses will be unblinded."; "will be conducted on a continuous basis and" added into the sentence "The planned preliminary analyses will focus purely on PK (no efficacy or safety outcomes will be analysed at that time)", and "Available PK data will be provided to the SMC for consideration when evaluating the safety of the trial." added after the sentence; "Final PK analyses and ("Fast-track") PK/PD analyses will be reported once after availability of data from DBL 1." removed after "No formal interim report will be generated."; "upon request" removed after "The SMC will review unblinded data"; "upon request by SMC" removed after "The independent statistician of the SMC will receive the randomization code to allow the required analyses on unblinded data".

Rationale for change		FDA recommended 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 6 to 17 years of age is comparable to adults, so the study procedures have been updated to meet this requirement. The specification "non-trial" will make clear that the personnel from the sponsor involved in the PK analyses is independent from the study team.
Section to be changed		8.7 Administrative structure of the trial
Description of change		"members of the BI trial team and trial independent members" replaced by "external experts independent from the trial and selected BI non-trial team members"; "PK and" added to the sentence "A SMC composed of … will be established to review individual and aggregated PK and safety data at regular intervals to determine the safety profile and risk/benefit ratio and recommend dose modification, additional assessments (e.g. laboratory tests), appropriateness of further enrolment and continuation/modification/premature interruption of the study".
Rationale for change		To clarify the independence of SMC members from trial team, and specify that the SMC will review PK data in addition to safety data.
Section to be changed		1.4.2 Risks
Description of change		Added "review individual and aggregated PK and safety data at regular intervals,", "about the appropriateness of further enrolment and continuation/modification/premature interruption of the study", and "dose modification and/or additional assessments (e.g." to the sentence "The SMC will review individual and aggregated PK and safety data at regular intervals, advise the study team about the appropriateness of further enrolment and continuation/modification/premature interruption of the study, and might recommend dose modification and/or additional assessments (e.g. intermediate checks in those patients who switched from placebo to nintedanib at the end of the initial 24 weeks of treatment)."
Rationale for change		To specify actions expected from SMC to mitigate the risk.

Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Added Table 4.2.2.1: 1 Restrictions regarding use of potent P-gp and CYP3A4 inhibitors and inducers.
Rationale for change		FDA recommended to exclude P-gp and CYP3A4 inducers per nintedanib prescribing information, so the restriction regarding use of potent P-gp and CYP3A4 inhibitors and inducers has been added to address the concerns raised, and minimize potential impact of these co-medications on the primary PK endpoint.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Added into criterion 13 the exclusion of patients with documented allergy to soya
Rationale for change		The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland recommended to exclude patients with documented allergy to soya per contraindications reported in the Investigator's Brochure.
Section to be changed		1.2 Drug profile, 1.3.1 Similarities and differences in the condition between populations and pharmacological rationale, 1.4.1 Benefits, 4.1.2 Selection of doses in the trial and dose modifications, 9.2 Unpublished references
Description of change		Updated reference to the current Investigator's Brochure (IB) Nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis, Progressive Fibrosing Interstitial Lung Disease.
Rationale for change		Updated version of the referenced documents has become available.
Section to be changed		1.2 Drug profile
Description of change		Added results from the study in adults with PF-ILD.
Rationale for change		Results from the study in adults with PF-ILD have become available.
Section to be changed		1.2 Drug profile, 1.3 Rationale for performing the trial, 1.4.1 Benefits, 9.1 Published references
Description of change		Added references to the recently published results from the study in adults with PF-ILD.
Rationale for change		Results from the study in adults with PF-ILD have become available.
Section to be changed		1.4.1 Benefits
Description of change		Section updated to state that nintedanib for SSc-ILD application has been approved in Europe, US and other countries; an application for an indication for nintedanib in adults with chronic

		fibrosing interstitial lung diseases with a progressive phenotype is approved in the US and other countries, and received a positive opinion in Europe; results of the INBUILD® trial are available.
Rationale for change		Regulatory status has changed, and results from the study in adults with PF-ILD have become available.
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		"Monitory" amended to "Monitoring", and statement about implementation of a protocol amendment if additional PK data are needed replaced by detailed information about the process to be followed and PK samples to be collected if additional PK data are needed.
Rationale for change		To amend a typo, and avoid a further protocol amendment.
Section to be changed		7.2.2 Primary endpoint analyses
Description of change		Added details about the analysis of the primary endpoint AUCτ,ss, and that further details on the PK analysis will be specified in the TSAP.
Rationale for change		Clarify how PK data will be used in the primary PK analysis.
Section to be changed		7.2.7 Interim Analyses
Description of change		Added information about update of primary analysis in case PK data are not sufficient and further PK data are collected.
Rationale for change		Clarify that if PK data collected for the primary analysis are not sufficient, then further PK data will be collected, the primary analysis will be updated and reported in the revision of the clinical trial report based on data from DBL 2.
Section to be changed		2.1.3 Secondary endpoints
Description of change		Added that the secondary endpoint "Change in height, sitting height, leg length from baseline at week 24, and week 52*" is also assessed at week 76*, and week 100*, but these time points will not be available for all patients.
Rationale for change		Clarify procedures and remove inconsistency with protocol synopsis.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		

Description of change		[redacted]
Rationale for change		Share the information available at the time of the current amendment.
Section to be changed		5.2.7.2.2 AE reporting to the sponsor and timelines
Description of change		"via fax" removed and "country specific contact details" replaced by "country specific reporting process".
Rationale for change		Adhere to changed corporate procedure and foresee submission of SAE forms by other means than fax.
Section to be changed		5.6.1 Assessment of quality of life via PedsQL™
Description of change		"and site staff" removed after "The PedsQL™ should be completed in a quiet area/room before the respondents complete any other health data forms and before they see the investigator"
Rationale for change		The patient will see the site staff before completion of the questionnaire as the site staff will administer the questionnaire.
Section to be changed		5.6.6 Assessment of HRCT
Description of change		"will" replaced by "might" in the sentence "In addition to confirmation of the presence of relevant fibrosis, visual and potentially quantitative analyses of the screening HRCTs might be performed to explore potential predictors of clinical outcomes".
Rationale for change		Clarify that these analyses might also not be performed, if not possible to perform.
Section to be changed		5.6.6 Assessment of HRCT
Description of change		With regards to HRCTs added "screening" and specified that the same acquisition protocol specifications should be followed when possible for screening HRCTs.
Rationale for change		Clarify that in some circumstances (e.g., historical HRCTs or when the devices used at a site is different from the standard referred to by the acquisition protocol) it might not be possible to follow the acquisition specifications defined by protocol.
Section to be changed		5.6.6 Assessment of HRCT, [redacted]
Description of change		Maximum duration of storage specified for HRCT scans updated to "30 years", [redacted]

Rationale for change		Provide updated information aligned with current standard procedures for data storage.

[redacted]

Section to be changed		Flow Chart
Description of change		Weeks under x visit changed from "64 plus Q12w" to "52 plus Q12w". Days under x visit changed from "449 plus Q84d ±7" to 365 plus Q84d±7".
Rationale for change		To ensure consistency with flowchart footnote 16: "Imaging follow-up will be conducted … at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter ... Dental examination (clinical) …. Follow-up will be conducted in all patients at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter … Dental imaging (panoramic x-ray) …. Follow-up will be conducted in all patients at 24 weeks, 52 weeks and every 48 weeks thereafter …".
Section to be changed		6.2.2 Treatment period: Visits 4, 5, 6, 8, 9, X (treatment period); 6.2.3 Follow-up period and trial completion
Description of change		Frequency of bone imaging follow-up changed from "every 3 months, and every 6 months after the first year" to "at 12 weeks, 24 weeks, 36 weeks, 52 weeks and every 24 weeks thereafter …". Frequency of dental examination follow-up (clinical) changed from "every 3 months, and every 6 months after the first year" to "at 12 weeks, 24 weeks, 36 weeks, 52 weeks, and every 24 weeks thereafter …". Frequency of dental imaging follow-up changed from "every 6 months, and every 12 months after the first year" to "at 24 weeks, 52 weeks, and every 48 weeks thereafter …".
Rationale for change		Clarify schedule of trial procedures and ensure consistency with Flow Chart footnote.

Section to be changed		6.2.2 Treatment period
Description of change		"A scheduled visit (V3-Vx)" replaced by "The first visit after the EoT visit" as subject of the sentence "will be skipped if the EoT visit occurs within 4 weeks prior to the scheduled visit."
Rationale for change		Clarify trial procedures and ensure consistency within Flow Chart footnote (**).
Section to be changed		Flow Chart footnote 16, 5.2.5 Assessment of pathological findings of epiphyseal growth plate, 5.2.6 Assessment of pathological findings on dental examination or imaging, 6.2.2 Treatment period
Description of change		"who qualified for randomisation" added after "will be conducted in all patients" for MRI/x-ray, dental examination, and dental imaging.
Rationale for change		Specify that these procedures will only be done if patient qualified for randomization, to avoid unnecessary procedures.
Section to be changed		6.2.2 Treatment period: Visit 2 (baseline)
Description of change		About the conduct of MRI/x-ray, dental examination, dental imaging at Visit 2, replaced "immediately before or after" with "immediately after" in the sentence "If it's not possible to conduct this procedure on the day of the visit, the procedure can be done in the weeks immediately after the visit". At the end of the sentence added a reference to the HRCT acquisition protocol available in the ISF for details.
Rationale for change		Amend the information as these procedures should not be done before Visit 2, and refer the investigator to the Image Acquisition Guideline for details.
Section to be changed		6.2.2 Treatment period: Visits 4, 5, 6, 8, 9, X (treatment period); 6.2.3 Follow-up period and trial completion
Description of change		About the conduct of MRI/x-ray, dental examination, dental imaging at Visits 4, 5, 6, 8, 9, X and in patients who prematurely discontinued trial medication, at the end of the sentence "If it's not possible to conduct this procedure on the day of the visit, the procedure can be done in the weeks immediately after the visit" added a reference to the HRCT acquisition protocol available in the ISF for details.
Rationale for change		Refer the investigator to the Image Acquisition Guideline for details.

[redacted]

Section to be changed		Title page
Description of change		Trial acronym added in brackets after the BI Trial No.
Rationale for change		Specify trial acronym.
Section to be changed		8.7 Administrative structure of the trial
Description of change		Purpose of the Disease Review Committee (DRC) amended from "To determine what percent of screen patients met protocol criteria for inclusion" to "To determine how well the protocol inclusion criteria were able to identify the intended population". Word "for" added to "… central reading for all patients evaluated for study participation at Visit 1".
Rationale for change		Amend incorrect information ensuring consistency with the DRC Charter, and clarify the following sentence.
Section to be changed		8.3.1 Source documents
Description of change		Missing words and commas added to the following sentences: "Copies of source documents necessary for the purposes of the trial will be provided to the relevant committee/vendor, as listed below: to the Disease Review Committee for retrospective evaluation of patients' characteristics compared to protocol inclusion criteria, to the Adjudication Committee for the adjudication of defined events, to the Safety Monitoring Committee for the evaluation of possible efficacy signals and for monitoring of safety throughout the conduct of the study, to the external radiology expert for central reading of HRCTs, to the external pathology expert for central reading of biopsies, to the external radiology expert for central reading of bone MRIs/x-rays, to the external paediatric dentistry expert for central reading of panoramic x-rays."

Rationale for change		Add text which was missing due to a technical issue.
Section to be changed		6.2.1 screening
Description of change		Removed ")"
Rationale for change		Typo

11.2 GLOBAL AMENDMENT 2

Date of amendment		14 Jun 2021
EudraCT number **EU number**		2018-004530-14
BI Trial number		1199-0337 (InPedILD™)
BI Investigational Medicinal Product(s)		Ofev®, nintedanib
Title of protocol		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
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Flow Chart, Flow Chart footnote 12, 6.1 Visit Schedule, 6.2.2 Treatment period
Description of change		In Flow Chart added to Visit 6 the procedure of IMP administration during the visit. In Flow Chart footnote 12 changed sentence to state that Part B will start once the first open label dose has been taken in the morning during the visit. In Section 6.1 specified that also the morning dose at Visit 2 and Visit 6 should be taken at the site. In section 6.2.2 specified that blood draw prior to administration of trial medication is applicable to Visit 2 and Visit 6 only, and that for the timing of blood draws to be conducted at Visit 3 and Visit 7 the Flow Chart for PK blood sampling should be referred to. Also specified that at Visit 6 the first dose of the open label trial medication will be administered at the site, then the patient's acceptability questionnaire will be administered. In preparation to Visit 6 the patient and parent(s)/legal guardian will be instructed that on the day of this visit the

		morning dose of trial medication should not be taken before going to the site, because the morning dose will be taken during the visit.
Rationale for change		At Visit 6 the study medication should be taken at site to ensure monitoring of possible immediate adverse reactions in those patients who received placebo during Part A and will receive their first dose of active medication at Visit 6.
Section to be changed		Flow Chart, Flow Chart footnote 9, Table 1.4.2:1, 5.2.3 Safety laboratory parameters, 6.2.2 Treatment period, 6.2.3 Follow-up period and trial completion
Description of change		Removed from Follow-up Visit the procedure to review the pregnancy test diary card and dispense the diary card together with urine dipstick pregnancy test. Specified that pregnancy testing will be conducted on blood at visits until end of treatment, and that at the Follow-up Visit the pregnancy test will be conducted on urines (if acceptable). Specified that test results will be documented in the patient's records. In case of positive results, procedures defined in Section 5.2.7.2.3 should be followed. Amended the sentence in section 6.2.2 with addition of bold words and removal of strikethrough words: "**Urine dipstick pregnancy tests and a**~~A~~ pregnancy test diary card will be dispensed **(females only)**; the patient and parent(s)/legal guardian will be instructed on how **the test should be conducted, and the diary** should be completed, **until**~~in the three days before~~ the next visit."
Rationale for change		At the Follow-up Visit the pregnancy test will be conducted on urines to make test results available immediately. Amend incorrect information given in Section 6.2.2.
Section to be changed		Flow Chart footnote 6, 6.2.3 Follow-up period and trial completion
Description of change		Specified that in case of clinically relevant changes of laboratory tests at EoT, lab tests will be repeated at follow-up unless the patient is enrolled into the open label extension trial.
Rationale for change		Clarify that laboratory tests with clinically relevant changes at EoT will be repeated only in

		patients who do not roll-over to the open label extension trial.

[redacted]

Section to be changed		Flow Chart footnotes
Description of change		Added a sentence to state that the interval between Visit 1 and Visit 2 could be >28 days.
Rationale for change		In some circumstances 28 days between Visit 1 and Visit 2 might not be sufficient to complete screening procedures.
Section to be changed		Flow Chart footnote 2, 5.2.5 Assessment of pathological findings of epiphyseal growth plate, 5.2.6 Assessment of pathological findings on dental examination or imaging, 5.6.6. Assessment of HRCT, [redacted] 6.2.1 screening, 6.2.2 treatment period, 6.2.3 Follow-up period and trial completion, [redacted]
Description of change		"(HRCT) acquisition protocol" replaced by "image acquisition guideline".
Rationale for change		Ensure consistency with the image acquisition guideline filed in ISF.
Section to be changed		Flow Chart footnote 16

Description of change		Specify that the time window for the baseline bone imaging, dental examination, dental imaging is 2 weeks after Visit 2, and that the time window for the follow-up bone imaging, dental examination, dental imaging is 1 week before or after the visit. Replaced "examination" with "dental imaging".
Rationale for change		Provide also in the Flow Chart footnote the information that these assessments could be made on a day close to the visit. To make clear that the sentence refers to dental imaging.
Section to be changed		Flow Chart for PK blood sampling, 5.3.1 Assessment of pharmacokinetics, 6.2.2 Treatment period
Description of change		Added to the Flow Chart for PK blood sampling and Section 5.3.1 a sentence to state that in rare circumstances PK sampling might need to be repeated (blood samples not taken at required timepoint, wrong medication taken in the days before PK sampling or on the day of PK sampling, destroyed/lost sample during shipment). In such cases PK sampling will be repeated close before the end of treatment visit, to allow the maximum possible interval from the previous PK sampling. Specified in Section 6.2.2 that PK sampling may occur, and PK diary card may be dispensed, at a different visit in case PK sampling needs to be repeated.
Rationale for change		As assessment of pharmacokinetics (PK: AUCτ,ss based on sampling at steady state (at week 2 and week 26)) is (next to assessment of safety) the main objective of the trial and the included patient population is small, every effort should be conducted to obtain all required samples for an appropriate and comparable PK analyses. This includes the exceptional possibility to repeat PK sampling if initial samples cannot be used.
Section to be changed		Abbreviations
Description of change		Added abbreviations.
Rationale for change		New words have been introduced with the current amendment.
Section to be changed		1.2 Drug Profile
Description of change		Removed sentence "This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present." after "The Residual Effect Period (REP)

		of nintedanib for the paediatric programme is 28 days."
Rationale for change		Remove incorrect information, as the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present is shorter than 28 days.
Section to be changed		1.3 Rationale for performing the trial
Description of change		Changed order of diseases mentioned.
Rationale for change		Add clarity.
Section to be changed		1.3.1 Similarities and differences in the condition between populations and pharmacological rationale
Description of change		Added "chronic" before "HP". Replaced "severe forms" with "progressive form" with regards to IPF.
Rationale for change		Be more accurate.
Section to be changed		1.4. Benefits
Description of change		Provided updated information about registration status.
Rationale for change		Registration obtained in further countries.
Section to be changed		1.4.2 Risks
Description of change		Removed "safety" from the sentence "Currently there is no experience with nintedanib in the paediatric population".
Rationale for change		Make clear that there's also no experience on efficacy in this population.
Section to be changed		1.4.2 Risks
Description of change		Added narrative text to describe reported adverse reactions associated with the use of nintedanib in adults and risks specific for the paediatric population based on preclinical animal studies; added heading to table.
Rationale for change		Provide additional information about reported adverse reactions and risks specific for the paediatric population based on preclinical animal studies.
Section to be changed		Table 1.4.2:1 Overview of trial related risks, Section 5.2.7.1.4 Adverse events of special interest
Description of change		Added pathological findings identified on bone imaging to the list of adverse events of special interest, and added expedited reporting of pathological findings identified on bone imaging to Table 1.4.2:1.
Rationale for change		Ensure expedited reporting from site to pharmacovigilance and timely reporting to SMC.

Section to be changed		Table 1.4.2:1 Overview of trial related risks, Section 5.2.7.1.4 Adverse events of special interest
Description of change		Added stunted growth identified on dental imaging to the list of adverse events of special interest, and added expedited reporting of stunted growth identified on dental imaging to Table 1.4.2:1.
Rationale for change		Ensure expedited reporting from site to pharmacovigilance and timely reporting to SMC.
Section to be changed		Flow Chart footnotes, 1.4.2 Risks, Table 1.4.2:1 Overview of trial related risks, 4.1.4 Drug assignment and administration of doses for each patient, 6.1 Visit schedule, 8.3.2 Direct access to source data and documents, Appendix 10.9 Visit modification in exceptional circumstances
Description of change		Added risks associated to the conduct of the study during the COVID-19 pandemic. Added mitigation measures and protocol modifications that can be implemented at a site.
Rationale for change		The COVID-19 pandemic has added risks associated with patient's visits at the site; mitigation measures and possible protocol modifications have been defined.
Section to be changed		8.3.2 Direct access to source data and documents
Description of change		Added sentence about remote and centralized monitoring.
Rationale for change		In case site access is restricted, some activities on site such as on-site source data review and source data verification may be performed remotely or replaced by centralized monitoring.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Added that there are no restrictions for trial participants to receive vaccination for COVID-19 during or after study treatment period.
Rationale for change		Clarify that vaccination for COVID-19 is allowed.
Section to be changed		[redacted]
Description of change		[redacted]

		[redacted]
Rationale for change		
Section to be changed		3.1 Overall trial design and plan, 3.2 Discussion of trial design, including the choice of control group, 7.2.7 Interim analyses, 7.5 Determination of the sample size
Description of change		Added words in bold: "The first DBL will be announced once 30 patients (at least 20 adolescents aged 12-17 years, **and if feasible at least 10 children aged 6-11 years**) have completed PK sampling at 26 weeks, or prematurely discontinued the trial…".
Rationale for change		Specify that the study will also try to complete PK sampling in 10 children aged 6-11 years.
Section to be changed		3.1 Overall trial design and plan, 3.2 Discussion of trial design, including the choice of control group, 7.2.7 Interim Analyses
Description of change		In Section 3.1 added words in bold "Based on the data from DBL 1 **(or updated DBL 1 data once the number of patients with sufficient PK data has been reached)**, the primary analysis/updated primary analyses and a benefit-risk assessment will be done and the clinical trial report for the primary analysis will be written. The timing of final DBL (DBL 2) and EoT visit will be communicated after confirming adequacy of PK data from DBL 1 **(or updated DBL 1)**." and "In the rare case that additional PK data is deemed necessary to complete the primary PK assessment, **data from DBL 1 will be updated and** the administrative DBL 2 will be postponed". In Section 3.2 added words in bold: "All PK and clinical data available at DBL 1 **(or updated DBL 1)** will be used in the primary analysis to allow for more robust estimates of exposure and potential treatment effect."

		In Section 7.2.7 Interim Analyses the following words have ben removed: "the primary analysis will be updated and reported in the revision of the clinical trial report based on data from DBL 2".
Rationale for change		Clarify that, in case after DBL1 further PK data are needed, a data snapshot will be taken once further PK data have been collected, and data based on DBL 1 will be updated.
Section to be changed		3.2 Discussion of trial design, including the choice of control group and 7.5 Determination of the sample size
Description of change		Added words in bold "study enrolment **into the treatment phase** will remain open until …" in Section 3.2, and "patient recruitment **into the treatment phase** will remain open until …" in Section 7.5.
Rationale for change		Make clear that enrolment into the treatment phase will be closed once the defined milestone is met.
Section to be changed		4.1.2 Selection of doses in the trial and dose modifications
Description of change		Added "Treatment should be interrupted in case the patient experiences a weight decrease below 13.5 kg. Treatment can be resumed when patient's weight reaches the threshold of 13.5 kg."
Rationale for change		Specify procedures to be followed in case of in case of patient's weight decrease below 13.5 kg.
Section to be changed		4.1.2 Selection of doses in the trial and dose modifications
Description of change		Added: "In case of pathological findings identified on follow-up bone imaging, or stunted growth identified on follow-up dental imaging, treatment should be interrupted, the patient case presented to the SMC by the sponsor and recommendations for next steps obtained. Treatment may be resumed upon recommendation of the SMC."
Rationale for change		Provide instructions about requirements in case these AESIs are reported: treatment interruption, evaluation by SMC and recommendation from the SMC before treatment can be resumed.
Section to be changed		Table 4.1.2: 2 Allowed treatment reduction / interruption periods
Description of change		Added "other events" as possible cause for treatment interruption.
Rationale for change		Treatment interruption might be caused by events other than AEs.
Section to be changed		Table 4.1.2:2 Allowed treatment reduction / interruption periods

Description of change		Changed text to clarify that IMP interruption should be max 4 weeks, while re-escalation to the dose assigned per Table 4.1.2: 1 may occur any time per investigator judgement.
Rationale for change		Clarify that IMP interruption should be max 4 weeks, while re-escalation to the dose assigned per Table 4.1.2: 1 may occur any time per investigator judgement.
Section to be changed		Table 4.1.2: 5 Recommendations for managing liver enzyme elevations
Description of change		The wording regarding withdrawal and interruption of trial medication has been revised.
Rationale for change		Clarify the information given.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Added words in bold: "One reserve wallet will be dispensed at Visit 2 **and at Visit 6**, and replaced as needed (e.g. in case of dose change requiring unit strength change, or use-by-date before the date planned for the next clinic visit) thereafter. **At Visit 6 any remaining wallet, including reserve, dispensed to the patient while the patient was taking part in the double-blind part of the study will be collected, and open label wallets will be dispensed.**"
Rationale for change		Specify that at Visit 6 a new reserve wallet will be dispensed to the patient, and any remaining wallet from the double-part of the study will be collected from the patient.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Added "To obtain kits with smaller capsules, an unscheduled visit should be registered in IRT. Once smaller capsules have been assigned, IRT will not allow to switch back to bigger capsules."
Rationale for change		Provide instructions about how to obtain smaller capsules in case the patient is not able to swallow big capsules.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Added "If contact with the content of the capsule occurs, hands should be washed immediately and thoroughly."
Rationale for change		Add recommendation implemented in the updated version of the IB.
Section to be changed		4.1.5.1 Blinding

Description of change		Removed "and Blinded Report Planning Meeting minutes".
Rationale for change		Procedures have changed.
Section to be changed		4.1.5.1 Blinding
Description of change		Added "No individual unblinding information will be shared, however it could be communicated to the trial team how many patients with evaluable PK data are missing to reach the target."
Rationale for change		Specify that the trial team could be informed about how many patients with evaluable PK data are missing to reach the target.
Section to be changed		4.1.5.2 Unblinding and breaking the code
Description of change		Added that in case the automated unblinding option via the IRT system is malfunctioning, the treatment allocation can be obtained contacting the IRT service provider, per instructions provided in the ISF.
Rationale for change		Clarify how to obtain unblinded information in case the IRT system is malfunctioning.
Section to be changed		Flow Chart, 5.1.2 Assessment of SpO_2, 6.2.1 Screening
Description of change		Specification that earlobe or forehead probes should be used has been removed. In Section 5.1.2 it has been specified that forehead probe is recommended, but if not available earlobe and finger probe are also allowed, as far as they are used consistently in the same patient.
Rationale for change		Earlobe or forehead probes suitable for the pediatric population are not available in all countries. Expert in ChILD confirmed that any probe can be used, if used consistently.
Section to be changed		Flow Chart, 5.1.2 Assessment of SpO_2, 6.2.2 Treatment period
Description of change		In the Flow Chart and Section 6.2.2 specified that continuous pulsoximetry (SpO_2) will be conducted during the 6MWT. In Section 5.1.2 specified that "SpO_2 with exertion will be measured during the 6MWT. See Section 5.1.6 for details."
Rationale for change		Specify that also SpO_2 with exertion will be measured, and that the 6MWT includes continuous pulsoximetry (SpO_2).
Section to be changed		5.2.6 Assessment of pathological findings on dental examination or imaging
Description of change		Added "Dental cone beam computed tomography can be conducted only in case panoramic x-rays cannot be performed, as far as it allows the same

		assessments, it is conducted according to the image acquisition guideline, and the same device is used consistently in the same patient."
Rationale for change		Specify that dental cone beam computed tomography is permitted under special conditions.
Section to be changed		[redacted]
Section to be changed		5.6.1 Assessment of quality of life via PedsQL™
Description of change		Added "If during the trial a patient changes age group, then the questionnaire appropriate for that age group should be administered."
Rationale for change		Clarify which questionnaire should be administered in case the patient changed age group during the trial.
[redacted]		[redacted]
Section to be changed		6.2.2 Treatment period, Visit 2 (baseline)
Description of change		About possible patient re-screening specified that to register patient's re-screening the site personnel should perform a re-screening call/notification in IRT; this way the patient will be assigned a new patient number linked to the original patient number. Specified also that re-screening of a previously screen failed patient will be permitted once.
Rationale for change		Provide further information about re-screening procedures and guide the investigator through the actions needed to associate the patient number assigned at re-screening with the patient number assigned at initial screening.

Section to be changed		Flow Chart footnotes, 6.2.2 Treatment period, End of Treatment visit
Description of change		Added: "Patients who did not discontinue trial treatment prematurely should undergo the EoT visit as soon as the timing of final DBL (DBL 2) and EoT visit has been communicated (see Section 3.1 for details). If a regular study visit is scheduled in the period when the EoT visit should be conducted, all procedures required at this regular study visit and the additional procedures, if any, required at the EoT visit will be conducted during the same visit."
Rationale for change		Ensure procedures required at scheduled visits are completed in case a regular study visit is scheduled in the period when the EoT visit should be conducted.
Section to be changed		6.2.2 Treatment period, End of Treatment visit
Description of change		Added a paragraph about offering participation in a separate open label extension trial.
Rationale for change		Guide the Investigator to complete this procedure at the proper time. Offering participation in a separate open label extension trial is mentioned in the protocol synopsis, but not in the list of procedures to be completed before the EoT visit.
Section to be changed		6.2.2 Treatment period, End of Treatment visit
Description of change		Added that at the EoT visit the site personnel will perform a call in IRT to register patient's end of treatment, and that returned wallets will be collected.
Rationale for change		Remind the site staff about the call in IRT and about the collection of study medication required at the EoT visit.
Section to be changed		7.2.1 General considerations
Description of change		Amended the definition of PKS with addition of bold words and removal of strikethrough words: Pharmacokinetic **Parameter Analysis** Set (PKS): The Pharmacokinetic **Parameter Analysis** Set (PKS) includes all **patients**~~subjects~~ in the Treated Set (TS) **who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a patient will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment.** ~~with at least one evaluable PK plasma~~

		~~concentration (referring to PK plasma concentrations not excluded due to an important protocol violation relevant for PK evaluation)~~. **Descriptive and model based analyses of PK parameters**~~Analyses for PK endpoints~~ will be based on the PKS. All other analyses will be based on the TS.
Rationale for change		Clarify PKS.
Section to be changed		7.2.2 Primary endpoint analyses
Description of change		Amended the sentence with addition of bold words and removal of strikethrough words: "For the primary PK analysis, the area under the plasma concentration-time curve at steady state (AUCτ,ss) will be calculated by ~~a~~ non-compartmental **as well as compartmental analysis ~~approach~~** and descriptive statistics will be provided as detailed in Section 7.2.1."
Rationale for change		Specify that compartmental analysis will also be conducted.
Section to be changed		8.7 Administrative structure of the trial
Description of change		Amended the information about how the SMC will access safety readings and bone/dental images.
Rationale for change		The SMC will have no contact with the central readers; reports and images will be provided to the SMC via CRO.
Section to be changed		8.7 Administrative structure of the trial
Section to be changed		Added "A Steering Committee will provide scientific advice on the clinical development program of nintedanib in the paediatric population. Tasks and responsibilities are defined in a contract."
Section to be changed		Specify that a Steering Committee will be consulted about the clinical development program of nintedanib in the paediatric population.
Section to be changed		8.7 Administrative structure of the trial
Description of change		Words "central images services" replaced with "… central imaging services …"
Rationale for change		Amend a typo.
Section to be changed		9.2 Unpublished references
Description of change		Updated reference to the IB.
Rationale for change		A new IB version has been released since the last version of the protocol.
Section to be changed		10.2 Creatinine clearance
Description of change		Added SI units in Appendix 10.2.
Rationale for change		SI units have been added for countries using SI.

APPROVAL / SIGNATURE PAGE

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Title: 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

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	14 Jun 2021 14:25 CEST
Author-Trial Statistician		14 Jun 2021 15:51 CEST
Approval-Clinical Pharmacokinetics		15 Jun 2021 08:24 CEST
Approval-Therapeutic Area [redacted]		15 Jun 2021 08:36 CEST
Approval-Team Member Medicine		15 Jun 2021 08:59 CEST
Verification-Paper Signature Completion		15 Jun 2021 14:04 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**