Clinical Trial Protocol

Document Number:	**c34797766 / 228892_978711_6.0**
EU Trial No. Universal Trial Number	2024-515743-27-00 U1111-1305-7514
BI Trial No.	1199-0378
BI Investigational Medicinal Product(s)	Ofev®, nintedanib
Title	An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON)
Lay Title	A study to evaluate long-term safety of nintedanib in children and adolescents with interstitial lung disease (InPedILD®-ON)
Clinical Phase	III
Clinical Trial Leader	[redacted]
Coordinating Investigator	
Current Version and Date	Version 6.0, 27 Nov 2024
Original Protocol Date	17 Jun 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	17 Jun 2021
Revision date	27 Nov 2024
BI trial number	1199-0378
Title of trial	An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON)
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre trial conducted in approximately 23 countries
Clinical phase	III
Trial rationale	The rationale of this open label trial is to collect additional safety and efficacy data of nintedanib in children and adolescents with clinically significant fibrosing ILD for at least 3 years (applies to patients rolling over from the parent trial) or until alternative treatment options become available or are made available (e.g., via marketing authorization, via compassionate use or via similar process) (applies to new patients and to roll-over patients after 3 years).
Trial objective(s)	The main objective of the trial is to assess the safety and tolerability of long-term treatment with nintedanib in pediatric patients with clinically significant fibrosing ILD.
Trial endpoints	The primary endpoint is the incidence of treatment emergent adverse events over the whole trial.
Trial design	Open label trial
Total number of patients entered	Approximately 50 to 60 patients
Number of patients per treatment group	Not applicable
Diagnosis	Clinically significant fibrosing ILD
Main inclusion and exclusion criteria	Patients who have completed the 1199-0337 (InPedILD®) study and did not prematurely discontinue trial treatment or Patients (children and adolescents ≥6 and ≤17 years old except in France (adolescents ≥12 and ≤17 years old)) with clinically significant fibrosing ILD who meet the following eligibility criteria: Main inclusion criteria: 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 eGFR <30 mL/min/1.73m^2, and/or underlying chronic liver disease (Child Pugh A, B or C hepatic impairment) at Visit 1; significant pulmonary arterial hypertension, any cardiovascular disease excluded by protocol, history of thrombotic event within 12 months of Visit 1, bleeding risk**.**
Test product(s)	nintedanib
dose	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) or 25 mg b.i.d. (50 mg daily). The dose assigned is based on patient's weight. Dose reduction 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)	Not applicable
dose	Not applicable
mode of administration	Not applicable
Duration of treatment	Treatment duration for each patient will be variable. For roll-over patients: at least 3 years; or until alternative treatment options become or are made available (e.g., via marketing authorization, via compassionate use, or via similar process) to the patient outside of the clinical trial. For new patients: until the overall end of the trial (with expected minimum treatment duration of 76 weeks). Exception: patients aged 21 years must complete the trial before their 22nd birthday. Consequently, a treatment duration of at least 3 years might not be reached by some patients aged 21. The overall end of trial will take place approximately when last roll-over patient is expected to reach 3 years of treatment [redacted]) ensuring that nintedanib or alternative treatment options (e.g., via marketing authorization, via compassionate use, or via similar process) will be available for all remaining patients (roll-over or new patients) outside the trial at this time.
Statistical methods	Descriptive statistics will be provided for adverse events [redacted].

FLOW CHART V1-V11

Trial Periods	**Screening**	**Treatment[3]**																		
Visits	**1[1]**	**2**	**3[4]**	**3a[3&4]**	**4**	**4a[3]**	**5**	**5a[3]**	**6**	**6a[3]**	**7**	**7a[3]**	**8**	**8a[3]**	**9**	**9a[3]**	**10**	**10a[3]**	**11**	**11a[3]**
Weeks[2]	-4		2		12		24		36		52		64		76		88		104	
Days[2]	≤28d before D1	D1[2]	15		85		169		253		365		449		533		617		729	
Time window for visits (days)		none	±3		±3		±3		±7		±7		±7		±7		±7		±7	
Informed consent and assent[5]	X																			
HRCT sent to central review[6]	X																			
Biopsy sent to central review[7]	X																			
Demographics	X																			
Medical history	X																			
Baseline conditions[8,]	X																			
[redacted]	X[30]																			
Physical examination, Vital signs[9]	X	X	X		X		X		X		X		X		X		X		X	
Height (standing and sitting)[10]	X	X			X		X		X		X		X		X		X		X	
Leg length		X			X		X		X		X				X				X	
Weight[10]	X	X	X		X		X		X		X		X		X		X		X	
12 lead-ECG (at rest)[11]	X	(X)					X				X				X				X	
Safety Laboratory (blood and urine)[12]	X[9]	X	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)
Pregnancy tests[13]	X	X	X		X		X		X		X		X		X		X		X	
Dispense urine pregnancy test with Diary Card (if applicable)[13]		X[13]	X[13]		X		X		X		X		X		X		X		X	
Review Diary Card for urine pregnancy test (if applicable)[13]					X		X		X		X		X		X		X		X	
[redacted]		X			X		X		X		X									

Trial Periods	**Screening**	**Treatment[3]**																		
Visits	**1[1]**	**2**	**3[4]**	**3a[3&4]**	**4**	**4a[3]**	**5**	**5a[3]**	**6**	**6a[3]**	**7**	**7a[3]**	**8**	**8a[3]**	**9**	**9a[3]**	**10**	**10a[3]**	**11**	**11a[3]**
Weeks[2]	-4		2		12		24		36		52		64		76		88		104	
Days[2]	≤28d before D1	D1[2]	15		85		169		253		365		449		533		617		729	
Time window for visits (days)		none	±3		±3		±3		±7		±7		±7		±7		±7		±7	
[redacted]	X	X	X		X		X		X		X		X		X		X		X	
FVC[15]	X	X	X		X		X		X		X		X		X		X		X	
D_{LCO}[15]		X																		
[redacted]		X									X								**X**	
Review of in-/ exclusion criteria	X	X																		
IRT call/ notification[17]	X	X	X		X		X		X		X		X		X		X		X	
Administer trial drug		X	X[18]		X[18]		X[18]													
[redacted]		X[14]			X[18]															
[redacted]			X[18]		X[18]		X[18]													
Dispense trial drug		X	X		X		X		X		X		X		X		X		X	
Collect trial drugs			X		X		X		X		X		X		X		X		X	
Compliance check/ drug accountability			X		X		X		X		X		X		X		X		X	
Criteria for dose reduction/ interruption check		X[29]	X		X		X		X		X		X		X		X		X	
[redacted]			X				X													
[redacted]		X					X				X				X				X	
[redacted]		X					X				X				X				X	
[redacted]		X	X		X		X		X		X		X		X		X		X	
[redacted]		X	X		X		X		X		X		X		X		X		X	
[redacted]		X	X		X		X		X		X		X		X		X		X	

Trial Periods	**Screening**	**Treatment[3]**																		
Visits	**1[1]**	**2**	**3[4]**	**3a[3&4]**	**4**	**4a[3]**	**5**	**5a[3]**	**6**	**6a[3]**	**7**	**7a[3]**	**8**	**8a[3]**	**9**	**9a[3]**	**10**	**10a[3]**	**11**	**11a[3]**
Weeks[2]	-4		2		12		24		36		52		64		76		88		104	
Days[2]	≤28d before D1	D1[2]	15		85		169		253		365		449		533		617		729	
Time window for visits (days)		none	±3		±3		±3		±7		±7		±7		±7		±7		±7	
Bone imaging (if applicable)[21]		ON REGULAR BASIS (Q12W to Q48W)[21]																		
Dental examination[22]		ON REGULAR BASIS (Q12W to Q24W)[22]																		
Dental imaging[23]		ON REGULAR BASIS (Q24W to Q48W)[23]																		
All AEs/ SAEs/AESIs	X	X	X		X		X		X		X		X		X		X		X	
Concomitant therapy [redacted]	X	X	X		X		X		X		X		X		X		X		X	
Vital status data[25]							(X)[25]				(X)[25]				(X)[25]				(X)[25]	

FLOW CHART V12 - END OF STUDY

Trial Periods	**Treatment[3]**											**Follow-up**
Visits	**12**	**12a[3]**	**13**	**13a[3]**	**14**	**14a[3]**	**15**	**15a[3]**	**X**	**Xa[3]**	**EoT[24, 30]**	**F-up[25] /EoS[26, 30]**
Weeks[2]	116		128		140		156		156 + Q12w			EoT +4wks
Days[2]	813		897		981		1093		1093+ Q84			EoT +28
Time window for visits (days)	±7		±7		±7		±7		±7			+7
[redacted]											X[30]	X[30]
Physical examination, Vital signs[9]	X		X		X		X		X		X	X
Height (standing and sitting)[10]	X		X		X		X		X		X	(X)[26]
Leg length			X				X		X /Q24w		X	
Weight[10]	X		X		X		X		X		X	(X) [26]
12 lead-ECG (at rest)[11]			X				X		X /Q24w		X	
Safety Laboratory (blood and urine)[12]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)[26]
Pregnancy tests[13]	X		X		X		X		X		X	X
Dispense urine pregnancy test with Diary Card (if applicable)[13]	X		X		X		X		X			
Review Diary Card for urine pregnancy test (if applicable)[13]	X		X		X		X		X		X	
[redacted]	X		X		X		X		X		X	X
FVC[15]	X		X		X		X		X		X	X
[redacted]							X				X	
IRT call/ notification[17]	X		X		X		X		X		X	
Dispense trial drug	X		X		X		X		X			
Collect trial drugs	X		X		X		X		X		X	
Compliance check/ drug	X		X		X		X		X		X	

Trial Periods	**Treatment[3]**											**Follow-up**
Visits	**12**	**12a[3]**	**13**	**13a[3]**	**14**	**14a[3]**	**15**	**15a[3]**	**X**	**Xa[3]**	**EoT[24, 30]**	**F-up[25] /EoS[26, 30]**
Weeks[2]	116		128		140		156		156 + Q12w			EoT +4wks
Days[2]	813		897		981		1093		1093+ Q84			EoT +28
Time window for visits (days)	±7		±7		±7		±7		±7			+7
accountability												
Criteria for dose reduction/ interruption check	X		X		X		X		X			
[redacted]			X				X		X/Q24w		X	
			X				X		X/Q24w		X	
	X		X		X		X		X		X	
	X		X		X		X		X		X	X
	X		X		X		X		X		X	X
Bone imaging (if applicable)[21]	ON REGULAR BASIS (Q12W to Q48W)[21]										X[24]	
Dental examination[22]	ON REGULAR BASIS (Q12W to Q24W)[22]										X[24]	
Dental imaging[23]	ON REGULAR BASIS (Q24W to Q48W)[23]										X[24]	
All AEs/ SAEs/AESIs	X		X		X		X		X		X	X[27]
Concomitant therapy [redacted]	X		X		X		X		X		X	X
Vital status data[25]			(X)[25]				(X)[25]		X/Q24w			(X)[25]
Completion of patient participation[28]							(X)[28]		(X/Q24)[28]			X[28]

1. **For new patients**, 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 (from informed consent signature to Visit 2) must not be longer than 12 weeks.

   For roll-over patients, Visit 1 and Visit 2 should occur the same day as EoT in InPedILD® 1199-0337 trial. In this case, all common procedures (e.g. physical examination, vital signs, height, leg length, weight, pregnancy test, ECG, [redacted], spirometry and some laboratory tests) will be performed once. If a patient is unable to roll-over on the day of EoT in 1199-0337 InPedILD® due to medical reason or in case the site is not ready to be initiated, the patient can be permitted to roll-over within 8 weeks following EoT. The interval between EoT and Visit1/Visit 2 or Visit 1 and Visit 2 may be extended at the discretion of Sponsor on a case-by-case basis.

2. Weeks and Days from the Day 1 (day of Visit 2).

3. During treatment period:

   - 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). Blood and urine sampling may be collected at the investigational site, primary care physician (GP, Pediatrician or Pulmonologist) or external laboratory preferably with specific study kits sent to the central laboratory for analysis or analysed locally.
   - Additional visits/ Phone calls (if appropriate) have to be included, in case of dose change (reduction or re-escalation) or in case of capsule's size change. Please refer to Section 6.2.2.
   - Additional visits may be needed for following safety assessments: bone imaging, dental examination and dental imaging. Please refer to footnotes 21, 22, 23.
   - Patients aged 21 years must complete the trial while being 21 years old. They should perform EoT visit and EoS visit (28 days after) before their 22nd birthday.

4. **For new patients:** Visit 3 applicable. For new patients in Norway, the Visit 3a is also applicable and should be performed at Week 6 (Day 43)

   For roll-over patients < 26 weeks (switching from InPedILD® to open label extension trial before Visit 7 (week 26)): Visit 3 applicable.

   For roll-over patients ≥ 26 weeks (switching from InPedILD® to open label extension trial at Visit 7 (week 26) or after): Visit 3 not applicable.

5. 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/given after the informed consent (and assent where applicable) was given, have to be recorded, including those that occurred between informed consent and Visit 1. Upon obtaining informed consent, the patient/parent(s)/legal guardian will be instructed on procedures to be followed until the next study visit.

6. **For new patients who didn't previously participate in InPedILD® only** - Central review of High-Resolution Computed Tomography (HRCT) for meeting inclusion criteria. One HRCT should not be older than 12 months. If the patient does not have an 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 at discretion of the investigator for the purposes of participation in the trial, provided the patient meets all other in-/exclusion criteria. For details about HRCT review, see Section 3.3.2.1.

7. **For new patients who didn't previously participate in InPedILD® only** - Central review of previous documented biopsy for meeting inclusion criteria. For details about biopsy review, see Section 3.3.2.1.
8. Medical conditions that are occurring concomitantly at Visit 1 will be recorded as baseline conditions in the electronic Case Report Form eCRF.
9. Measurements of vital signs should precede blood sampling, [redacted]
10. 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 eCRF. An average of the 3 measurements will be calculated.

    For new patients who didn't previously participate in InPedILD®: height and weight assessed in the 2 years prior to screening (Visit 1) will also be collected, if available.
11. Electrocardiogram (ECG) at rest (if possible, prior to blood sampling) will be performed at Visit 1 and at visits specified in the Flow Chart thereafter (every 24 weeks).

    For new patients, it will be repeated at Visit 2 prior to treatment allocation only if abnormal at Visit 1.
12. **For new patients,** the safety laboratory tests of Visit 1 must be repeated if interval between Visit 1 and Visit 2 is longer than 6 weeks.
13. Pregnancy testing should be conducted in all female patients, even pre-menarche, every 4 weeks. Pregnancy blood test will be conducted at each scheduled visit until EoT. At the Follow-up/EoS Visit, the pregnancy test will be conducted on urines (if acceptable). Additionally, urine pregnancy test should be repeated at home or at a local laboratory / local doctor, every 4-6 weeks if applicable, between clinic visits 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. In case of premature treatment discontinuation, when patient continues with visits off treatment, the pregnancy tests at home (for female patients) are only required to be continued every 4 weeks for the 3 months after last trial drug intake.

    From Visit 2 for roll-over patients ≥ 26 weeks and from Visit 3 for new patients and for roll-over patients < 26 weeks, urine dipstick pregnancy tests will be provided with pregnancy test diary card when needed. Use of pregnancy test diary card will be explained with the patient / parent(s)/legal guardian 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. Pregnancy test diary card will be reviewed at clinic visits. 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.
14. [redacted]
15. **For new patients:** Order of lung function measurements: 1. FVC followed by patient's rest; 2. D_{LCO}.

    For roll-over patients, D_{LCO} not applicable.

    For all patients: after Visit 2 FVC measurements to be done at the same time each visit (+/- 90 min), with reference time at Visit 2.
16. [redacted]
17. Interactive Response Technology (IRT) should be notified upon obtaining informed consent.

18. [redacted]

    Please refer to Appendix 10.1 for details.

19. [redacted]

20. [redacted]

21. Bone imaging. Please refer to Section 5.2.5 and to the image acquisition guideline available in the ISF for details. For patients aged 19 and older, please see additional information at the end of the footnote.

For new patients: Bone imaging is required for all new patients who qualified for assignment of nintedanib treatment at Visit 2 as baseline. If it's not possible to conduct the baseline bone imaging at Visit 2, the procedure can be done in the 2 weeks immediately after the visit (until D15).

Imaging follow-up will be conducted only in patients with open physes at predefined time points. Imaging follow-up will be conducted, if applicable, at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks, 128 weeks, 156 weeks, and every 24 weeks thereafter until the end of study or closure of the physes. If it's not possible to conduct the follow-up at the predefined time points, the procedure can be done within 1 week before and after this time point with always minimum of 10 weeks (during the first year)/22 weeks (thereafter) and always maximum of 16 weeks (during the first year)/28 weeks (thereafter) between 2 procedures.

For roll-over patients: Bone imaging procedure is not applicable for patients with closed physes at the end of InPedILD®. For all other roll-over patients, previous MRIs/x-rays of epiphyseal growth plates within 12 weeks (for roll-over patients with treatment duration less than 52 weeks in InPedILD®) and within 24 weeks (for roll-over patients with treatment duration more than 52 weeks in InPedILD®) prior Visit 2 should be used as baseline in the analyses of bone imaging (for scheduling of follow-up procedures see next paragraph). If a previous MRI/x-ray as outlined above, is not available, an MRI/x-ray should be conducted at Visit 2. If it's not possible to conduct it at Visit 2, the procedure can be done in the 2 weeks immediately after the visit (until D15).

Irrespective of scheduled visits, imaging follow-up will be conducted only in patients with open physes, every 12 weeks in the year after the start of the trial medication in the parent trial (when applicable) and every 24 weeks thereafter until the end of the study or closure of the physes.

If it's not possible to conduct the follow-up at the predefined time points, the procedure can be done within 2 weeks before and 4 weeks after this time point with always a minimum of 10 weeks (during the first year after the start of the trial medication in the parent trial)/22 weeks (thereafter) and always a maximum of 16 weeks (during the first year after the start of the trial medication in the parent trial)/28 weeks (thereafter) between 2 procedures.

Preponement or postponement of one follow-up procedure by 2 months to the planned timepoint will be allowed once to align this procedure and the subsequent ones with the regular clinic visits planned in the protocol. After this alignment, the acceptable time window will be +/-1 week for this procedure (as for new patients).

For patients aged 19 and older, bone imaging follow-up procedures will be performed around every 48 weeks (instead of around every 24 weeks) until the end of the study or closure of the physes.

For all patients, if the follow-up procedure cannot be conducted at least every 16 weeks (during the first year)/28 weeks (thereafter), the study treatment of this individual patient needs to be interrupted upon discussion with the sponsor (except for the one-time alignment with clinic visits mentioned above for roll-over patients).

For all patients, timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.

22. Clinical dental examination. Please refer to Section 5.2.6.

For new patients: Clinical dental examination is required according to protocol requirements in all new patients who qualified for assignment of nintedanib treatment at Visit 2 as baseline. If it's not possible to conduct the baseline clinical dental examination at Visit 2, the procedure can be done in the 2 weeks immediately after the visit (until D15).

Follow-up will be conducted, if applicable, at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks, 128 weeks, 156 weeks, and every 24 weeks thereafter until the end of the study. If it's not possible to conduct the follow-up at the predefined time points, the procedure can be done within 1 week before and after this time point with always maximum of 16 weeks (during the first year)/28 weeks (thereafter) between 2 procedures.

For roll-over patients: Previous dental examination at 1199-0337 EoT or within 12 weeks prior Visit 2 should be used as baseline in the analyses of clinical dental examinations (for scheduling of follow-up procedures see next paragraph). If a previous dental examination is not available, this examination should be conducted at Visit 2. If it's not possible to conduct the dental examination at Visit 2, the procedure can be done in the 2 weeks immediately after the visit (until D15).

Irrespective of scheduled visits, follow-up will be conducted, every 12 weeks in the year after the start of the trial medication in the parent trial (when applicable) and every 24 weeks thereafter until the end of the study.

If it's not possible to conduct the follow-up at the predefined time point, the procedure can be done within 2 weeks before and in the 4 weeks after this time point with always a maximum of 16 weeks (during the first year after the start of the trial medication in the parent trial)/28 weeks (thereafter) between 2 procedures.

Preponement or postponement of one follow-up procedure by 2 months to the planned timepoint will be allowed once to align this procedure and the subsequent ones with the regular clinic visits planned in the protocol. After this alignment, the acceptable time window will be +/-1 week for this procedure (as for new patients).

For all patients, if the follow-up procedure cannot be conducted at least every 16 weeks (during the first year)/28 weeks (thereafter year), the study treatment of this individual patient needs to be interrupted upon discussion with the sponsor (except at the one-time alignment with clinic visits mentioned above for roll-over patients).

For all patients, timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.

23. Dental imaging. Please refer to Section 5.2.6 and to the image acquisition guideline available in the ISF for details.

For new patients: Dental imaging is required according to protocol requirements in all patients who qualified for assignment of nintedanib treatment at baseline (Visit 2). If it's not possible to conduct the dental imaging on the day of the Visit 2, the procedure can be done in the 2 weeks immediately after the visit (until D15).

Follow-up will be conducted, if applicable, at 24 weeks, 52 weeks,104 weeks, 156 weeks, and every 48 weeks thereafter until the end of the study. If it's not possible to conduct the follow-up at the predefined time points, the procedure can be done within 1 week before and after this time point with always a minimum of 22 weeks (during the first year)/46 weeks (thereafter) and always a maximum of 28 weeks (during the first year)/52 weeks (thereafter) between 2 procedures.

For roll-over patients: Previous dental imaging at 1199-0337 EoT or within 24 weeks prior EoT/Visit 1/Visit 2 should be used as baseline in the analyses of dental imaging (for scheduling of follow-up procedures see next paragraph). If a previous dental imaging is not available, this dental imaging should be conducted at Visit 2. If it's not possible to conduct the dental imaging on the day of the Visit 2, the procedure can be done in the 2 weeks immediately after the visit (until D15).

Irrespective of scheduled visits, follow-up will be conducted, every 24 weeks in the year after the start of the trial medication in the parent trial (when applicable) and every 48 weeks thereafter until the end of the study.

If it's not possible to conduct the follow-up at the predefined time point, the procedure can be done within 2 weeks before or 4 weeks after this time point with always a minimum of 22 weeks (during the first year after the start of the trial medication in the parent trial)/46 weeks (thereafter) and always a maximum of 28 weeks (during the first year after the start of the trial medication in the parent trial)/52 weeks (thereafter) between 2 procedures.

Preponement or postponement of one follow-up procedure by 2 months to the planned timepoint will be allowed once to align this procedure and the subsequent ones with the regular clinic visits planned in the protocol. After this alignment, the acceptable time window will be +/-1 week for this procedure (as for new patients).

For all patients, if the follow-up procedure cannot be conducted at least every 28 weeks (during the first year)/52 weeks (thereafter), the study treatment of this individual patient needs to be interrupted upon discussion with the sponsor (except for the one-time alignment with clinic visits mentioned above for roll-over patients).

For all patients, timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.

24. Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EoT) visit as soon as possible.

At the EoT visit:

- the MRI/x-ray should not be repeated if the last MRI/x-ray was conducted within 24 weeks,
- the dental examination will not be repeated if the last examination was conducted within 12 weeks and
- the dental imaging will not be repeated if the last examination was conducted within 24 weeks.

If EoT occurs before Visit 15 (week 156), roll-over patients will be asked to remain in the study and to return to all regularly scheduled visits until week 156. New patients who prematurely discontinued trial drug will be asked to remain in the study and to return to all regularly scheduled visits until the overall end of trial.

At future off-treatment visits, all assessments [redacted], and IRT call/notification will be performed. The first visit after the EoT visit will be skipped if the EoT visit occurs within 4 weeks prior to scheduled visit but if MRI/x-ray and/or dental examinations/imaging were planned at this visit, then they should be performed as planned. Only one additional regular follow-up for bone imaging and for dental imaging procedures will be needed after the EOT visit if there is no pathological finding. If there is a pathological finding, follow-up procedures will be conducted on individual basis upon discussion with the sponsor and with the investigator. Follow–up procedures for clinical dental examination will be conducted as initially planned by the protocol. Urine pregnancy tests at home (for female patients) are only required to be continued every 4 weeks for the 3 months after last trial drug intake.

25. For patients who discontinue trial treatment prematurely and are not able to complete the scheduled visits, a follow-up (FU) visit should be planned 28 days after EoT.

If the EoT visit has been delayed and has been done 28 days or more after the treatment discontinuation, the follow-up (FU) visit can be skipped.

In addition, every attempt will be made to get information on vital status, when applicable, at 24, 52, 76, 104, 128, 156, and every 24 weeks thereafter until the end of the study and for new patients at EoS. Please see Section 5.2.7.2.1

26. End of Study (EoS), synonym for individual patient's end of trial. Height, weight or safety laboratory test will be repeated at EoS visit in case of clinically relevant change at EoT. In exceptional cases, when the patient is not able to come at site for medical reason, the EoS visit can be replaced by a phone call. If the EoT visit has been delayed and has been done 28 days or more after the treatment discontinuation, the EoS visit can be skipped.
27. 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.
28. For patients who discontinue permanently trial treatment before Visit 15 and who accepted to attend further scheduled visits as per protocol, then the patient's trial completion will be at initial planned date of Visit 15 (at week 156) for roll-over patients and at the overall end of trial for new patients. Completion of trial participation will be conducted at EoT visit, if FU/EoS visit is skipped due to delayed EoT for more than 28 days.
29. For roll-over patients only

[redacted]

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

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ABBREVIATIONS AND DEFINITIONS

ABCA3	ATP Binding Cassette Subfamily A Member 3
AC	Adjudication Committee
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Products
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
ATS / ERS	American Thoracic Society / European Respiratory Society
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
ß-HCG	Beta- Human Chorionic Gonadotropin
BI	Boehringer Ingelheim
CA	Competent Authority
chILD	Childhood Interstitial Lung Disease
cHP	Chronic Hypersensitivity Pneumonitis
CNS	Central Nervous System
COHb	Carboxyhaemoglobin
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CSF1R	Colony-Stimulating Factor 1 Receptor
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager

CTP	Clinical Trial Protocol
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
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EDTA	Ethylenediamine-Tetraacetic Acid
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FGFR	Fibroblast Growth Factor Receptor
FUP	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastro-Intestinal
GLI	Global Lung Initiative
GMP	Good Manufacturing Practice
HA	Health Authority
[redacted]	
Hb	Haemoglobin
HP	Hypersensitivity Pneumonitis
HRCT	High-Resolution Computed Tomography
HSCT	Haematopoietic Stem Cell Transplant

i.v	Intravenous
IB	Investigator's Brochure
ICH	International Council 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
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
LFT	Liver Function Test
LPLT	Last patient last treatment
Lyn	Tyrosine-protein Kinase Lyn
MACE	Major Adverse Cardiovascular Events
MCTD	Mixed Connective Tissue Disease
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
n.a.	Not Applicable
NSIP	Non-Specific Interstitial Pneumonia
OPU	Operative Unit
PIP	Pediatric Investigational Plan
PAH	Pulmonary Arterial Hypertension
PBMC	Peripheral Blood Monocytic Cells
PDGFR	Platelet-Derived Growth Factor Receptor
[redacted]	
PF-ILD	Progressive Fibrosing Interstitial Lung Disease

P-gp	Permeability Glycoprotein
[redacted]	
PM	Polymyositis
[redacted]	
PT	Prothrombin Time
PTM	Planned Time
Q	Quaque i.e. every
q.d.	quaque die (once a day)
RA	Regulatory Authority
RA-ILD	Rheumatoid Arthritis associated ILD
RBC	Red Blood Count
REP	Residual effect period
SAE	Serious Adverse Event
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus 2
SFTPC	Surfactant Protein Deficiency
SI	International System of units
SMC	Safety Monitoring Committee
SMQ	Standard MedDRA Query
[redacted]	
SOP	Standard Operating Procedure
[redacted]	
Src	Proto-oncogene Tyrosine-protein Kinase
SSc-ILD	Systemic Sclerosis associated ILD
SUSAR	Suspected Unexpected Serious Adverse Reactions
TKI	Tyrosine Kinase Inhibitor
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
US	United States
VEGFR	Vascular Endothelial Growth Factor receptor

WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Childhood interstitial lung disease 'chILD' syndrome' is a term used to describe diffuse lung disease in children with non-specific respiratory symptoms. It consists of a heterogeneous group of rare respiratory diseases associated with varying morbidity and mortality [R09-5337]. Although many of the ILDs present in children can also be found in adults, some chILDs are specific to paediatric populations and involve different pathophysiology.

While the pathophysiology underlying most of the pediatric ILD have not been fully characterized, according to the expert opinion, the following diagnoses were considered to be most likely associated with chronic fibrosis and as such potentially amenable to anti-fibrotic treatments:
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.

There are no currently approved therapies for the treatment of ILD in children. Clinical management is focused on supportive care (e.g. oxygen therapy, ventilator support). Therapeutic treatment is primarily based on anecdotal evidence, such as case series and clinical observation. Based on the mode of action of nintedanib and its demonstrated effects in adult IPF and other chronic fibrosing ILDs with progressive phenotype, the use of nintedanib in fibrotic ILDs in children was considered to be of potential benefit.
As the underlying diseases associated with the clinically significant fibrosing Interstitial Lung Disease may be multiple, different regimes of immunosuppressives/ supportive symptomatic therapy are considered as standard of care for the treatment of ILD in children.

In the Phase III trial, InPedILD® (BI trial 1199-0337; EudraCT no. 2018-004530-14), the parent trial to this open label study, the dose-exposure relationship and safety of nintedanib in children and adolescents with fibrosing ILD was investigated and information on the efficacy was collected as well. In the parent trial, following completion of the 24-week blinded, placebo-controlled treatment period (Part A) patients entered a variable, open label treatment period (Part B). Once 30 patients (including at least 20 patients of age 12-17 years) completed PK at week 26, or prematurely discontinued, the first database lock was announced (DBL1).

As, the benefit/risk assessment based on the data of the InPedILD® trial justified further exposure to nintedanib, all patients still on treatment were offered to participate in this open label trial InPedILD®-ON (BI trial 1199-0378). Rollover of eligible patients from InPedILD®

study to the current trial was planned to occur without treatment interruption, whenever possible [c26450188].

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].

A soft gelatin capsule formulation of nintedanib is used in humans. After oral administration, nintedanib is absorbed quickly and has an absolute bioavailability of slightly below 5% in healthy volunteers.

Nintedanib displayed a high volume of distribution and a high total plasma clearance; the terminal half-life of nintedanib is in the range of 10 to 15 h. Nintedanib is mainly eliminated via faeces. The major metabolites are BIBF 1202 and its glucuronide. Nintedanib is a substrate and a weak inhibitor of P-gp.

For adults, nintedanib is available in two dose strengths corresponding to 100 mg and 150 mg. In the paediatric trial, a third dose strength of 25 mg is available, and nintedanib is

administered in doses of 150, 100, 75, or 50 mg bid depending on predefined weight categories.

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 4.2.1:1) [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, 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 pediatric 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].

Single dose toxicity studies in rats and mice indicated low acute toxic potential of nintedanib. In repeat dose toxicology studies in rats, adverse events (e.g. thickening of epiphyseal plates, lesions of the incisors) were mostly related to the mechanism of action of nintedanib (i.e. VEGFR-2 inhibition). Changes occurring during bone growth phases were reversible after discontinuation, while alterations in tooth structure and function were irreversible. These findings are considered class effects and may be particularly relevant for growing children with regards to development and growth of skeleton and teeth. Diarrhoea and vomiting, accompanied by reduced food consumption and loss of body weight, were observed in toxicity studies in non-rodents. There was no evidence of liver enzyme increases in rats, dogs, and cynomolgus monkeys. Mild liver enzyme increases were only observed in rhesus monkeys.

Nintedanib is non-mutagenic. Embryo-foetal lethality and teratogenic effects in rats were observed at dose level resulting in plasma drug concentrations comparable or below those in humans.

Data from clinical studies
Nintedanib (trade name: Ofev) is approved for the treatment of IPF and for the treatment of SSc-ILD in the US, EU, Japan and a large number of additional countries. Nintedanib is recently also approved in the US, EU, Japan, Canada and a number of other countries for the treatment of (chronic) fibrosing ILDs with a progressive phenotype.

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 adult 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 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 decrease 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 Investigator's Brochure (IB) Nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis and Progressive Fibrosing Interstitial Lung Disease [c01783972].

1.3 RATIONALE FOR PERFORMING THE TRIAL

The rationale of this open label trial is to collect additional safety and efficacy data of nintedanib in children and adolescents with clinically significant fibrosing ILD for at least 3 years (applies to patients rolling-over from parent trial) or until alternative treatment options become or are made available (e.g., via marketing authorization, via compassionate use, via similar process) (applies to new patients and to roll-over patients after 3 years).

Alternative therapies outside of the trial would be alternative drugs shown to have positive benefit-risk assessment, any new therapy which would be available on the market for this indication or most probably the availability of nintedanib via marketing authorization, or via compassionate use or via similar process, as offered/provided by the sponsor (depending on local laws).

It is expected that availability of nintedanib via marketing authorization, or via compassionate use or via similar process, as offered/provided by the sponsor (depending on local laws) occurs in most countries [redacted] However, roll-over patients should stay in the trial for at least 3 years and new patients should stay in the trial until the end of trial (with the exception of patients ≥ 22 years of age) to ensure collection of patient data for a prolonged period of time.

At individual level, this trial is aimed to provide nintedanib treatment for all patients who have completed InPedILD®, the parent trial, and who may have experienced benefit from the trial medication according to investigator judgement and wish to receive treatment.

In addition to patients rolled over from the InPedILD® study, in order to address the high unmet medical need for safe and efficacious treatment of this devastating condition, newly identified children and adolescents with clinically significant fibrosing ILD will enter this trial if they meet the eligibility criteria of the protocol.

Consequently, the patient population will include two cohorts: roll-over patients who have completed InPedILD® (and did not prematurely discontinue trial medication in InPedILD®) and newly recruited patients who meet the eligibility criteria of the current protocol including patients who discontinued treatment in InPedILD® but are again eligible (for details refer to section 3.1).

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Although the classification of paediatric interstitial lung disease is distinct from that of adult ILD, similar to adults with progressive fibrosing ILD, some patients with children's interstitial lung disease (chILD) develop chronic lung fibrosis that is associated with significant morbidity and mortality. However, there are currently no approved therapies for the treatment of fibrosing interstitial lung disease in children. Building on the scientific working hypothesis of the progressive fibrosing ILD programme that lung fibrosis can become progressive, self-sustaining independent of the original clinical association or trigger, it is postulated that targeted antifibrotic therapy may also provide therapeutic benefit in children with fibrosing lung disease. Based on the mode of action and demonstrated effect in various pre-clinical models of ILD, treatment of fibrosing ILDs with nintedanib in children

and adolescents is expected to lead to similar clinical benefit as in adults with fibrotic lung diseases.
In addition, this open label trial only started when the review of the first InPedILD® results had been completed and once the positive benefit/risk assessment justifies the start of this follow up open label study. The benefit/ risk was be assessed favorable if nintedanib-treated patients showed a comparable exposure to that observed in adults and the safety and tolerability of nintedanib was considered acceptable.

All patients will receive active treatment with nintedanib in this trial.

1.4.2 Risks

Currently, except in the ongoing parent trial, there is no experience with nintedanib treatment in the paediatric population. However, the known risks of use of nintedanib in adults can be 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 potential risks specific to the pediatric 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 (please see Table 1.4.2:1).

The most frequently reported adverse reactions associated with the use of nintedanib in adults, and the potential risks specific to the paediatric population, already identified for the parent trial, will be carefully monitored in the same way as in the parent trial. The same mitigation strategy as the one in place in the InPedILD® trial, outlined below, will apply for each potential risk /adverse event in 1199-0378 trial.

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 for worsening the disease course of COVID-19. However, patients with chronic fibrosing interstitial lung disease may be at risk of severe clinical courses due to 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 Investigational Medicine Product (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 [c01783972]		
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 (CTP Section 4.2.1.1), regular monitoring by SMC.
Decreased appetite	Same as above.	Weight check every 12-16 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 4.2.1.2), 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).
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 (Adverse Event of Special Interest (AESI)). Careful monitoring of liver function, guideline to liver enzyme elevations (CTP Section 4.2.1.2). 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,	Increased awareness and expedite reporting (AESI).

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	may result in fatal outcome.	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 in all female patients, even pre-menarche, every 4 weeks. Pregnancy blood test at each scheduled visit until EoT, with urine pregnancy tests repeated at home or at a local laboratory / local doctor, every 4 weeks between clinic visits until the end of the trial and at the EoS/Follow-up Visit (if acceptable). 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 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 on 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 12-16 weeks. Regular evaluation by SMC.
Impact on bone development and growth	In animal models, nintedanib has been shown to alter the epiphyseal growth plates of large	Monitor potential reversible effects on bone development and growth by:

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	bones (femur and tibia). Changes seen in rodents were: in epiphyseal growth plates (thickening due to increased number of hypertrophic chondrocytes) and articular cartilage (swelling of chondrocytes in the basal layers). These changes were reported during bone growth and were reversible after discontinuation.	Regular evaluation by radiology expert, with skeletal growth monitoring (MRIs or x-rays of epiphyseal growth plates) at baseline and regular follow-up conducted in patients with open physes at predefined time points until end of the study or closure of the physes (defined as 100% skeletal maturity) in patients with open physes. The follow-up bone imagings will be planned, irrespective of scheduled visits, in order to respect the frequency of around every 12 weeks for first year and around every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial. Please refer to Flow Chart footnotes and to CTP Section 5.2.5 for more details. Expedited reporting of pathological findings identified on bone imaging (AESI). Regular evaluation by SMC. Not applicable for roll-over patients with closed physes at the end of parent trial
Impact on dentition	In animal models, nintedanib has been shown to impact tooth development. Tooth changes were major with altered tooth structure and function which were irreversible. (In rodents (more prominently in the rat than in the mouse), nintedanib induced a pharmacologically mediated dentopathy	Monitor potential severe/irreversible effects on dentition by: Regular evaluation by dentist, with dental examination at baseline and regular follow-up conducted at predefined time points. The follow-up dental examinations will be planned, irrespective of scheduled visits, in order to respect the frequency of around every 12 weeks for first year and around every 24

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	(degeneration and loss of odontoblasts and ameloblasts with consecutive structural changes of enamel and cementum) of the continuously growing incisors often accompanied by dental fractures, hemorrhages and necroses in the pulp). Changes occurred only during the growth phase of the teeth.	weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial. Please refer to Flow Chart footnotes and to CTP Section 5.2.6 for more details. Expedited reporting of stunted growth identified on dental imaging (AESI). Regular evaluation by paediatric dentistry expert, with panoramic x-ray at baseline and and regular follow-up conducted at predefined time points. The follow-up dental imagings will be planned, irrespective of scheduled visits, in order to respect the frequency of around every 24 weeks for first year and around every 48 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial. Please refer to Flow Chart footnotes and to CTP Section 5.2.6 for more details. 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. For new patients: HRCT at baseline required only if acceptable HRCT not available within 12 months of Visit 1.

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
		[redacted] Bone MRI/x-ray required with always minimum 10 weeks (first year)/22 weeks (thereafter) and dental X-ray required with always minimum 22 weeks (first year)/46 weeks (thereafter) from the previous procedure, taking into account, for roll-over patients, the participation in the parent trial (except at the one time alignment of these safety procedures with clinic visits). Similarly, bone MRI/x-ray at EoT required only if previous MRI/x-ray not available within 12 weeks in the first year, 24 weeks thereafter. Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety. Panoramic x-ray at EoT required only if previous panoramic x-ray not available within 24 weeks.
Others risks		
Risk of contracting a SARS CoV-2 infection.	Travelling to the site or being at the site for trial visit may potentially increase the risk of contracting a SARS CoV-2 infection.	The number of site visits is limited to the minimum required for the successful conduct of 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, Section 6.2 and

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
		Appendix 10.9).

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

An external Safety Monitoring Committee (SMC) will ensure monitoring of safety throughout the conduct of the study. Further details on SMC and other external committees in Section 7.

1.4.3 Discussion

This open label trial only started recruiting once the first results of InPedILD® trial have been reviewed and justify the start of this open label trial by confirming that safety and tolerability of nintedanib is considered acceptable in the patient population of the InPedILD® trial.
The planned trial procedures and the associated risks are deemed acceptable, as they allow for timely identification of potential risks, interruption or discontinuation of treatment if required to manage adverse events/ adverse drug reactions.
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 extrapolated benefit-risk of nintedanib in the target population is considered acceptable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The trial will assess the safety and tolerability of long-term treatment with nintedanib in pediatric patients with clinically significant fibrosing ILD.

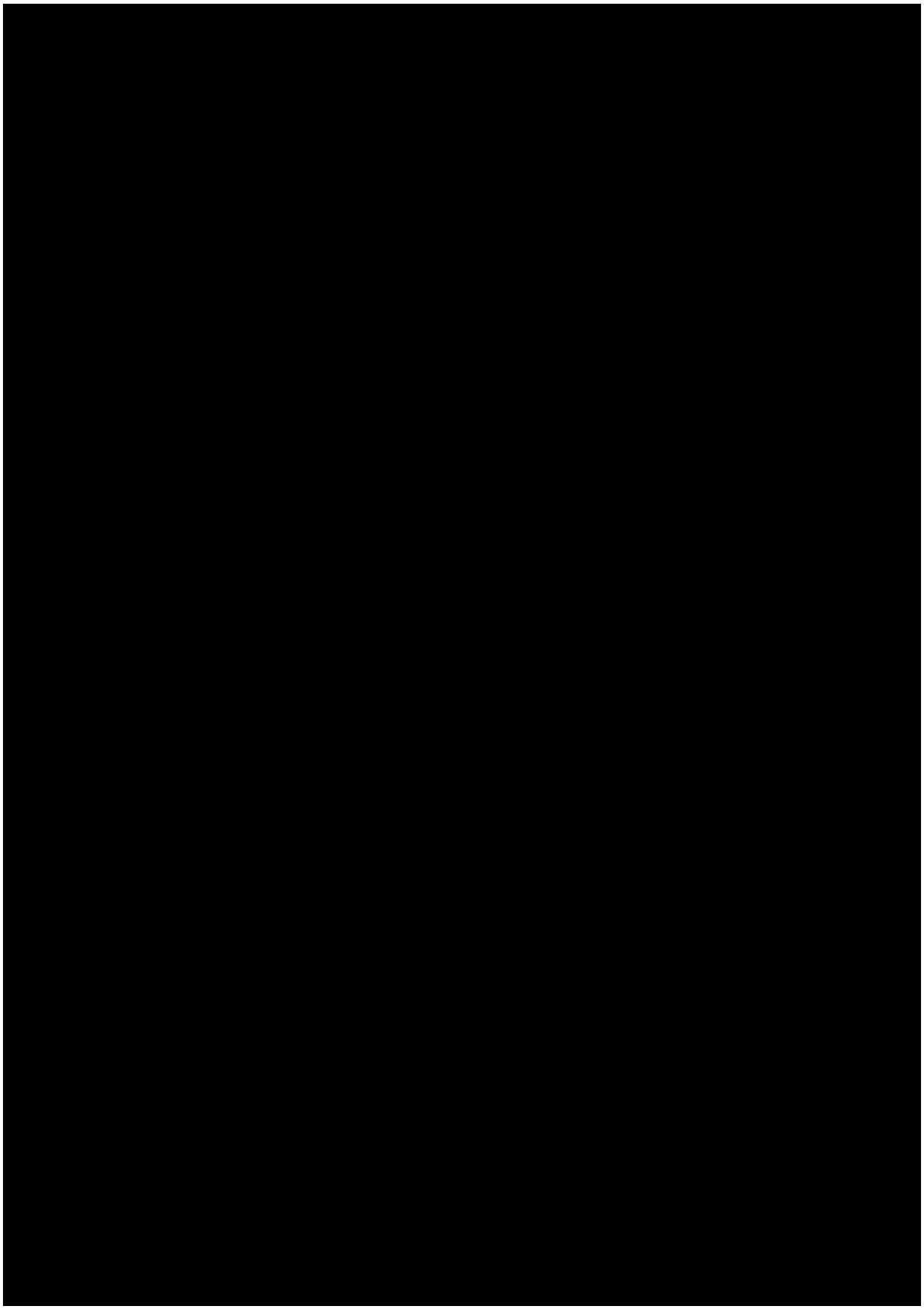
The primary objective is to estimate the incidence of treatment emergent adverse events over the whole trial.

2.1.2 Primary endpoint(s)

The primary endpoint is the incidence of treatment emergent adverse events over the whole trial.

2.1.3 Secondary endpoint(s)

No secondary endpoints are defined.



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a multi-centre, multi-national, not randomised, open label clinical trial.

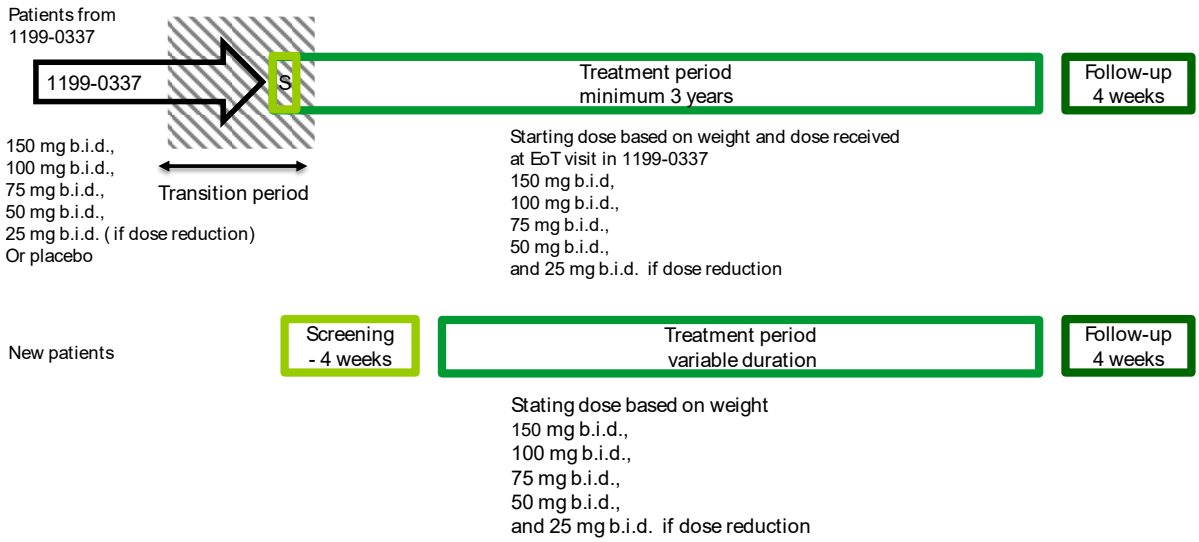


Figure 3.1:1 Trial design

The patient population will include two cohorts:
Patients rolling over from the InPedILD® study:
At the time point when the data from the InPedILD® trial are available, and a positive benefit risk assessment (by external independent SMC and internal BI Benefit Risk Committee) justifies the start of the current trial, all patients on study treatment (including those who temporarily interrupted treatment for less than 8 weeks) at the end of the parent trial InPedILD® will be offered participation in the current long-term study. These patients can be enrolled into 1199-0378 from Part A or from Part B.

Patient's individual benefit-risk to receive long-term treatment of nintedanib should be assessed by the investigator. The decision to participate in this study will be made by the patient/parent(s)/legal guardian following a discussion on this benefit-risk assessment with the investigator.

Completed patients from the parent trial not able to roll-over into the extension trial within 12 weeks following their End of Treatment Visit in the parent trial (i.e. time period between last dose of study drug in parent trial and first dose in extension trial is greater than 12 weeks) will formally not be considered as "roll-over" patient. These patients will be handled as new patients in 1199-0378, i.e. they have to follow the visit schedule for new patients but will have adapted inclusion/exclusion criteria (please refer to Section 3.3.2 and to Section 3.3.3).

Patients who prematurely permanently discontinued treatment due to AE considered related to nintedanib in the InPedILD® trial will not be eligible for this open-label trial.

Patients who permanently discontinued trial treatment due to AE considered related to placebo or for reasons other than drug-related AE and are willing to participate in study 1199-0378 will potentially be eligible for this open-label trial. For those patients, the individual benefit risk and potential eligibility for participation in study 1199-0378 should be carefully assessed by the investigator and should be discussed with the sponsor. These patients will be handled as new patients in 1199-0378, i.e. they have to follow the visit schedule for new patients.

Patients who have withdrawn consent to trial participation in InPedILD® will not be eligible for 1199-0378.

Whenever feasible, for roll-over patients, the first visits (Visit 1 and Visit 2) of this open-label trial should be on the same day as the End of Treatment visit of InPedILD®, the parent trial, to allow for continuous treatment. In this case, procedures performed at the EoT of InPedILD® should not be repeated if stated as planned at Visit 1 or Visit 2 in the 1199-0378 trial (please refer to section 6.2.1 and Flow Chart).

After signing Informed Consent, and if all eligibility criteria are met, patients will receive treatment with nintedanib at their last dose of study medication in the parent trial 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) or 25 mg b.i.d. (50 mg daily) unless the patient's weight has changed such that a different dose is required (please refer to Table 4.1.2: 1).
For those patients with dose reduced in the parent trial, the dose can be increased based on the judgement of the investigator. Similar to the parent trial, dose reduction to the next lower dose is possible to manage adverse events.
At the time point of start of this open label study, the treatment received by the patient in the parent trial in Part A remains blinded until the final DBL (DBL2) occurs for the parent trial.

Patients newly enrolled in the study:
Enrollment will also be open to newly identified children and adolescents with clinically significant fibrosing ILDs if they meet the eligibility criteria of the current protocol, or to patients who needed to discontinue trial treatment (due to AE considered related to placebo or for reason other than drug-related AE) in InPedILD® and again are eligible for treatment with nintedanib according to investigator's assessment (and after discussion with the sponsor).
All new patients recruited for the study will enter a 4-week screening period. After this first period, patients meeting in-/exclusion criteria will initiate their treatment period of the study.
Starting dose assigned will be based on patient's weight:
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).

For all patients, during treatment period, 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).

Roll-over patients will be requested to stay in the trial for at least 156 weeks (until Visit 15). At week 156, roll-over patients who can be treated with nintedanib or alternative treatment options outside the clinical trial will have their EoT Visit instead of Visit 15.

The remaining roll-over patients will continue in the trial until nintedanib or alternative treatment options can be made available to them outside the clinical trial.

New patients will be requested to stay in the trial until the end of trial (with expected minimum treatment duration of 76 weeks),
then patients will perform their EoT Visit and enter in the 28-days follow-up period off-treatment until End of Study Visit (EOS).

Exception: patients aged 21 years must complete the trial before their 22nd birthday. Consequently, a treatment duration of at least 3 years might not be reached by some patients aged 21.
Patients completing trial while being 21 years old, even with a treatment duration less than 3 years, will be considered as completed patients.

The overall end of trial will take place approximately when last roll-over patient is expected to reach 3 years of treatment ([redacted]) ensuring nintedanib or alternative treatment options (e.g., via marketing authorization, via compassionate use, or via similar process) will be available for all remaining patients (roll-over or new patients) outside the trial at this time.

At this time, all the remaining patients will perform their EoT Visit.
For logistical reasons, it may be planned that EoT visit of all remaining patients will occur within 6 weeks before the planned date of Visit 15 of last roll-over patient. If regular scheduled visit is planned for a patient during this period of 6 weeks, then the patient will skip this regular visit and will perform directly the EoT visit instead. After the EoT visit, all remaining patients will enter a 4-week follow-up period.

Trial medication will be stopped prematurely if a reason for withdrawal is met (refer to section 3.3.4).
Roll-over patients will be considered as prematurely discontinued from trial treatment if they stop trial medication before week 156 (except at the age of 21).
New patients will be considered as prematurely discontinued from trial treatment if they discontinue trial treatment before the overall end of trial (except at the age of 21).

Patients who prematurely discontinue trial medication should come to the clinic to perform EoT as soon as possible after treatment discontinuation.
Roll-over patients prematurely discontinued from trial treatment before week 156 will be asked to remain in the study and return to all regularly scheduled visits until Visit 15 (individual planned date of week 156).
New patients prematurely discontinued from trial treatment will be asked to remain in the study until the overall end of trial (expected to occur approximately when last roll-over patient is expected to reach 3 years of treatment).

For patients who prematurely discontinued trial drug and who are unable to complete the scheduled visits, a follow-up (FU) visit should be planned for 28 days after EoT. In addition, every attempt will be made to collect information on vital status, when applicable, at weeks

24, 52, 76, 104, 128 and 156 and for new patients at EoS. 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).

If it is intended by a treatment discontinued patient to use available nintedanib outside the trial after trial treatment discontinuation, the patient should directly undergo the EoS visit 28 days after the EOT visit (no vital status will be required for this patient).

A patient will be considered lost to follow-up if the investigator is not able to contact the patient/parent(s)/legal guardian despite multiple attempts. Every effort must be made; at least 2 telephone contacts plus 1 mailing should be documented. The site must notify the clinical monitor prior to designating a patient as lost to follow-up.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

All patients will receive active treatment as prolonged used of placebo would not be appropriate. The design as open label study with no comparison group is appropriate for assessing the long-term tolerability and safety of nintedanib in pediatric patients with fibrosing ILDs.
This trial will follow the study InPedILD® to address EMA's request on the collection of additional safety and efficacy data as discussed during the PIP negotiations.
In addition to patients rolled over from the InPedILD® study, in order to address the high unmet medical need for safe and efficacious treatment of this devastating condition, newly identified children and adolescents with clinically significant fibrosing ILD from already participating centres will have the possibility to enter in this trial if they meet the eligibility criteria.

[redacted]

3.3 SELECTION OF TRIAL POPULATION

It is anticipated that at least 30 patients on treatment at the end of the InPedILD® trial, from approximately 40 sites in about 21 countries, will consent to participate (and thus receive treatment (if eligible)) in this trial.
In addition, considering enrolment of 2 patients/month across around 40 sites, approximately 20 to 30 newly identified patients are expected to enter treatment in an estimated recruitment period of 18 months with a screen failure rate around 50%. Extension of the study population beyond that of the parent trial is aimed at addressing a high unmet medical need for safe and efficacious therapy for fibrosing ILDs in children and adolescents.

Re-enrolment of screen failed patients will be permitted once. Patients who did not qualify for entering treatment during the early months of the recruitment period might qualify for entering treatment during the late months of the recruitment period of the study. A new informed consent/assent will be signed by the patient/parent(s)/legal guardian and the patient

will be assigned a new unique patient number. The previous patient number will be collected via the electronic Case Report Form (eCRF).

A log of all patients enrolled into the trial (i.e. who have an informed consent signed) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.
If retrospectively it is found that a patient has been entered in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment by the investigator in discussion with the patient and its parents/legal guardian and discussion with the sponsor, a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

Main diagnosis for trial entry is identical with that of the parent trial i.e. clinically significant fibrosing ILD as defined by clinical and radiological criteria detailed below.

For patients who rollover from the parent trial InPedILD®, eligibility of these patients will be established based on a limited number of criteria listed below. Exceptionally, patients that reached adult age during participation of 1199-0337 will be allowed to participate in 1199-0378.
For newly recruited patients, all eligibility criteria based on InPedILD® study apply and are listed below.

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

For new patients:

1. Children and adolescents 6 to 17 years old at Visit 2. In France, only adolescents 12 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 CTP Section 4.2.2.3.

[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.

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.
5. Patients with FVC % predicted ≥25% at Visit 2.

   [Note: Predicted normal values will be calculated according to GLI (Global Lung Initiative)]
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
     - other measures of clinical worsening attributed to progressive lung disease (e.g. increased oxygen requirement, decreased diffusion capacity).

   Instructions on Fan score will be given in Appendix 10.2.

For roll-over patients from the InPedILD® study:
Only criteria 2 and 3 listed for new patients are applicable with the following additional inclusion criterion:

7. Patients who completed the InPedILD® trial as planned and who did not permanently prematurely discontinue study treatment.

For patients who prematurely discontinued treatment permanently in 1199-0337 but are potentially eligible and for completed patients from parent trial not able to roll over into the extension trial within 12 weeks following their End of Treatment Visit in the parent trial:
Inclusion criteria for new patients are applicable except criteria 4, and 6 (as eligibility for these criteria has been confirmed already in 1199-0337 and does not need to be repeated) and also except inclusion criterion 1 for completed patients from parent trial not able to roll over within 12 weeks following their End of Treatment Visit in the parent trial.

3.3.2.1 Evidence of fibrosing ILD for new patients:

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 required with at least one of the following imaging findings on one HRCT scan.

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.

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 but are not counted as features that confirm fibrosis. Co-existing multifocal non-fibrotic, non-dependent consolidations (e.g. organizing pneumonia, infection) will not be allowed.

For patients without any documented lung biopsy or whose biopsy results do not meet the biopsy criteria for fibrosis listed above, confirmation of fibrosis on two HRCT scans will be required.

At least two different findings of the following imaging findings are required on at least two HRCT scans (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.

Co-existing ground glass opacity is acceptable but is not counted as feature that confirms fibrosis. Co-existing multifocal non-fibrotic, non-dependent consolidations (e.g. organizing pneumonia, infection) will not be allowed.

3.3.3 Exclusion criteria

For new patients:

1. AST and/or ALT >1.5 x ULN at Visit 1.
2. Bilirubin >1.5 x ULN at Visit 1.
3. Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m^2 at Visit 1(please refer to Appendix 10.3).
   [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 the visit 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. Other investigational therapy received within 1 month or 5 half-lives (whichever is shorter but ≥1 week) prior to Visit 2 except investigational therapy received in InPedILD® trial.
6. 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
7. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
8. 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) (please refer to Appendix 10.5). Not applicable in France.
      ii. In adolescents 13 to 17 years old: systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg (please refer to Appendix 10.5). In France, applicable for adolescents 12 to 17 years old.
   b. Myocardial infarction within 6 months of Visit 1
   c. Unstable cardiac angina within 6 months of Visit 1
9. 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, as well as prophylactic use of 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

10. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1.
11. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin).
12. Patients with documented allergy to peanut or soya.
13. 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.
14. Life expectancy for any concomitant disease other than ILD <2.5 years (investigator assessment).
15. Female patients who are pregnant, nursing, or who plan to become pregnant while in the trial.
16. Patients not able or willing to adhere to trial procedures, including intake of study medication.
17. Patients who must or wish to take any drug considered likely to interfere with the safe conduct of the trial according to investigator's benefit-risk assessment for the individual patient
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).

<u>For roll-over patients from the InPedILD® study:</u>
Only criteria 11, 12, 13, 15, 16, 17 and 19, listed for new patients are applicable with the following additional exclusion criterion:

20. Patient not compliant in parent trial (InPedILD®), with trial medication or trial visits, according to investigator's judgement.

Roll-over patients may qualify for participation even though other exclusion criteria may have been met during the participation in InPedILD®, if the investigator's benefit-risk assessment for the individual patient remains favourable. This should be discussed with sponsor before the roll-over of patient.

<u>For patients who prematurely discontinued treatment permanently in 1199-0337 but are potentially eligible and for completed patients from parent trial not able to roll over into the extension trial within 12 weeks following their End of Treatment Visit in the parent trial:</u>
All exclusion criteria for new patients are applicable. In addition, the following additional exclusion criterion is applicable for patients who prematurely discontinued treatment permanently in 1199-0337:

21. Patients who experienced drug-related adverse events during parent trial leading to permanent study treatment discontinuation.

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or patient/parent(s)/legal guardian may withdraw consent/assent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and Section 3.3.4.2 below.
However, if the patients agree, they should stay in the trial even if continued trial treatment is not possible: roll-over patients should attend further trial visits until Visit 15 and new patients should attend until the overall end of trial to ensure their safety and 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 reporting (please see Section 5.2.7.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment or if parent(s)/legal guardian want(s) the patient to discontinue trial treatment. They will be asked to explain the reasons but have the right to refuse to answer.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he / she 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/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, as well as prophylactic use of 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 GI-bleeding or GI-ulcers.

In case of a temporary reason, trial treatment should be restarted if medically justified, please see Section 4.1.4

In case, the laboratory results at Visit 2 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 in the patient's medical records.

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

- The patient experiences signs of hepatic injury attributable to trial drug, 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 interferes with the safety of the investigational medicinal product or other trial treatment. Please refer to Sections 4.2.1 and 4.2.2.

The patient can no longer receive trial treatment for medical reasons such, adverse events, other diseases, or pregnancy.
If a patient becomes pregnant during the trial the investigational product must be interrupted immediately, and the patient will be followed up until birth of the child/children or otherwise termination of the pregnancy. The study medication may be only re-introduced once the child has been born and the mother is no longer nursing, if supported by individual benefit risk as judged by the investigator. 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 permanent 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 planned observation period. For those patients who are unable to complete the remaining scheduled visits, every attempt will be made to get information on vital status as outlined in the Flow Chart and Section 6.2.3.

If it is intended by a treatment discontinued patient to use available nintedanib outside the trial after trial treatment discontinuation, the patient should directly undergo to the EoS visit 28 days after the EOT visit (no vital status will be required for this patient).

If new efficacy / safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, instruct to pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

3.3.4.2 Withdrawal of consent to trial participation

Patient/parent(s)/legal guardian may withdraw their consent/assent to trial participation, at any time without the need to justify the decision.
If patient/parent(s)/legal guardian want(s) to withdraw consent/assent, the investigator should be involved in the discussion with the patient/parent(s)/legal guardian 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. [redacted]
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
4. [redacted]

Further treatment and follow up of patients affected will occur as described in Section 3.3.4.1.
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, and 25 mg. All patients will be treated with nintedanib in this trial; there is no active comparator or placebo.

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 paediatric population. The 75 mg and 50 mg doses will be provided as multiples of the 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

The investigational products will be provided by BI or a designated clinical research organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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.
Method and route 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] for details).

This approach was 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.

Confirmation or, if needed, adaptation of the dosing algorithm to achieve nintedanib exposure in pediatric patients comparable to the plasma exposure in adult IPF/SSc-ILD/ chronic fibrosing ILD of a progressive phenotype patients receiving the approved dose of nintedanib 150mg b.i.d. was a part of benefit/risk assessment to be performed in the Phase III parent study InPedILD® following DBL1.
Upon confirmation of the algorithm used in the 1199-0337 InPedILD® study, the doses of nintedanib will be assigned by body weight bin as shown in table below.

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

		InPedILD®	**1199-0378**	
Body weight bin – Provenance of patient	**Weight range****	**Last dose used (b.i.d.) and treatment groups**	**Dose (b.i.d.) and treatment groups**	**Dose reduction possibility (b.i.d.)**
1 - Patients from Part B of InPedILD®	13.5* to <23.0 kg	50 mg or 25 mg*** (nintedanib)	50 mg or 25 mg (nintedanib)	25 mg (nintedanib)
1 - Patients from Part A of InPedILD®	13.5 to <23.0 kg	50 mg or 25 mg*** (nintedanib/placebo)	50 mg or 25 mg (nintedanib)	25 mg (nintedanib)
1 - New patients	13.5 to <23.0 kg		50 mg (nintedanib)	25 mg (nintedanib)
2 - Patients from Part B of InPedILD®	23.0 to <33.5 kg	75 mg or 50 mg*** (nintedanib)	75 mg or 50 mg (nintedanib)	50 mg (nintedanib)
2 - Patients from Part A of InPedILD®	23.0 to <33.5 kg	75 mg or 50 mg*** (nintedanib/placebo)	75 mg or 50 mg (nintedanib)	50 mg (nintedanib)
2 - New patients	23.0 to <33.5 kg		75 mg (nintedanib)	50 mg (nintedanib)

		InPedILD®	**1199-0378**	
Body weight bin – Provenance of patient	**Weight range****	**Last dose used (b.i.d.) and treatment groups**	**Dose (b.i.d.) and treatment groups**	**Dose reduction possibility (b.i.d.)**
3 - Patients from Part B of InPedILD®	33.5 to <57.5 kg	100 mg or 75 mg** (nintedanib)	100 mg or 75 mg (nintedanib)	75 mg (nintedanib)
3 – Patients from Part A of InPedILD®	33.5 to <57.5 kg	100 mg or 75 mg** (nintedanib/placebo)	100 mg or 75 mg (nintedanib)	75 mg (nintedanib)
3 - New patients	33.5 to <57.5 kg		100 mg (nintedanib)	75 mg (nintedanib)
4 - Patients from Part B of InPedILD®	≥57.5 kg	150 mg or 100 mg** (nintedanib)	150 mg or 100 mg (nintedanib)	100 mg (nintedanib)
4 - Patients from Part A of InPedILD®	≥57.5 kg	150 mg or 100 mg** (nintedanib/placebo)	150 mg or 100 mg (nintedanib)	100 mg (nintedanib)
4 - New patients	≥57.5 kg		150 mg (nintedanib)	100 mg (nintedanib)

*patients < 13.5 kg of weight are excluded from the trial.
**Confirmation or, if needed, adaptation of the weight range in the algorithm will be part of benefit/risk assessment in InPedILD®.
***If dose already reduced in InPedILD® or if dose reduction is needed at visit 2. In these cases, no further reduction will be possible. However, for treatment interruption please refer to Section 4.2.1.

New patients:
The patient's weight will be measured at screening and at each IMP dispensing visit (see Flow Chart for details). 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.

Roll-over patients:
Patient will receive nintedanib at corresponding dose assigned in the parent trial, whether the patient was previously assigned to the nintedanib or the placebo treatment group. If the patient's weight has changed such that a different dose is required (please refer to Table 4.1.2: 1, the appropriate dose of nintedanib will be assigned.
For those patients who dose reduced in the parent trial, the dose can stay reduced or be increased based on the judgement of the investigator.

Similar to the parent trial, treatment interruption and dose reduction to the next lower dose are allowed to manage adverse events.

4.1.3 Method of assigning patients to treatment groups

An Interactive Response Technology (IRT) system will be used to screen eligible patients, perform drug assignment, register EoT and manage initial/re-supply ordering of drug supplies. The investigator will receive all necessary instructions to access the IRT from the Sponsor.
After the assessment of all in- and exclusion criteria, each eligible patient will receive treatment with nintedanib. The assigned dose of nintedanib will be based on the patient's weight at Visit 2 as shown in Table 4.1.2: 1.
IRT will be used to assign medication numbers to eligible patients until EoT or premature discontinuation. Details of IRT procedures can be found in the IRT manual located in the Investigator Site File (ISF).
The appropriate medication numbers will be assigned and documented in the eCRF. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

For an individual patient, the start of treatment period will be planned at Visit 2, and the end of treatment period is planned at the EoT Visit. The first dose of trial medication should be taken during the Visit 2 in the morning at the clinic and 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 via IRT contact during scheduled clinic visits detailed in the Flow Chart.

Each patient will receive active drug at dosage of 150 mg bid, 100 mg bid, 75 mg bid, 50 mg bid or 25 mg bid. Nintedanib will be administered orally on a twice daily basis.

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.

At each concerned visit, the number of dispensed wallets will be adapted to assure sufficient coverage until the next dispensing visit.

The investigational product should only be dispensed to parents/caregiver(s) (or patients if applicable based on their maturity) by authorized personnel as documented in the "Trial Staff List".

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, 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).

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 next dose should be taken as scheduled. 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 via IRT and instruct the patient/parent(s)/legal guardian on the number of capsules to be taken in the morning and in the evening until the next visit.
In case the start/end of an AE requires a dose reduction/increase without the need of a change in capsule size and without requiring a meeting with the investigator in person, the unscheduled visit for the patient can be replaced by a phone call. The investigator will register the phone call in IRT as an unscheduled visit and register the dose reduction/increase on the respective page in the eCRF.
Drug accountability will be completed carefully. Please refer to Section 6.2.2 for instructions.
If needed, an unscheduled visit can be registered in IRT at any time during the course of the trial to register a dose change, to obtain additional kit(s) or to obtain kits with smaller or larger capsules.

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

In this open-label trial, treatment allocation will not be concealed throughout the trial. The eCRF will contain information on actual treatment.

For patients coming from InPedILD®, the previous treatment received in InPedILD® part A (active drug or placebo) will remain unknown to the investigator and patient until after the

final database lock of InPedILD®. No individual unblinding regarding treatment received in InPedILD® should occur prior to this time.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated 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, i.e. capsules containing nintedanib, 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 Research Associate (CRA) (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 or delegate when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,
- Approval / notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- 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

Rescue medications to reverse the action of nintedanib are not available.

[redacted] during the trial will be recorded in the eCRF.

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-escalated after recovery.

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.

Only one reduced dose is possible for each body weight bin meaning that if patient is receiving already a reduced dose, no further dose reduction will be possible without re-increase before. Dose reduction and re-increase are allowed at multiple occasions.

The reduced dose per body weight bin is mentioned in Table 4.2.1:1. This should be considered to manage adverse events. No further dose reduction outside of those listed will be allowed.

Temporary treatment interruption is also allowed to manage adverse events.

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.

In case of persistent adverse events observed at the reduced dose, or severe effects at the starting dose for new patients, permanent treatment discontinuation should be considered.

The criteria to be followed for treatment interruption, re-start and re-escalation are shown in Table 4.2.1:1.

Table 4.2.1:1 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.

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.

To manage diarrhoea and liver enzyme elevations guidelines similar to the parent trial and based on guidelines in adult programme are provided.

4.2.1.1 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 anti-diarrhoeal symptomatic treatment, e.g. loperamide.
If diarrhoea persists despite optimal symptomatic treatment, treatment interruption and/or dose reduction of nintedanib should be considered. Table 4.2.1.1: 1 shows the recommendations for children and adolescents with the appropriate age and weight-adjusted dosing.

Table 4.2.1.1: 1 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 4.2.1.1: 2) 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 Visit 2.

Table 4.2.1.1: 2 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

4.2.1.2 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 4.2.1.2: 1 for patients.

Table 4.2.1.2: 1 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	
At Visit 2 for new patients (start of treatment)	Permanently discontinue trial medication or justify continuation[1]	Permanently discontinue trial medication	Permanently discontinue trial medication	Permanently discontinue trial medication
At any other Visit for new patients and At all visits for roll-over patients	Continue as planned[2]	Reduce dose or interrupt trial medication[3]	Interrupt trial medication	Interrupt trial medication (may subsequently need to be permanently discontinued[5])
		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**
	<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, preferably by using appropriate visit lab kit as instructed to site by the sponsor.
[5]Permanently discontinue after discussion with the sponsor if hepatic injury is a confirmed diagnosis and judged related to trial medication

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 preferably with specific trial lab kits sent to the central laboratory for analysis or analysed locally.

4.2.1.3 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).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

As detailed in the exclusion criteria, new 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). If it is intended by a treatment discontinued patient to use available nintedanib outside the trial after trial treatment discontinuation, the patient should directly undergo the EoS visit 28 days after the EOT visit (no vital status will be required for this patient).

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	
Ketoconazole, cyclosporine A (or ciclosporin), boceprevir, clarithromycin, conivaptan, erythromycin, indinavir, itraconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole.	NOT permitted: [redacted]
P-gp and CYP3A4 strong inducers	
Avasimibe, carbamazepine, phenytoin, rifampin	NOT permitted: [redacted]
Products including St. John's wort	NOT permitted: [redacted]

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, preferably by using intermediate (a-visit) trial lab kit are recommended.

Patients who are using a bronchodilator must have their spirometry performed according to the guidelines provided below:
- Withhold short–acting bronchodilators for at least 8 hours before the assessments,
- Withhold long–acting bronchodilators for at least 24 hours before the assessments.

In case of a patient forgets to withhold bronchodilator(s) intake in the morning of clinic visits, the study visit has to be rescheduled the day after.

4.2.2.2 Restrictions on diet and life style

There is no restriction 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 3.3.3) must use two medically approved methods of birth control throughout the trial, and until 3 months after last trial drug intake: one barrier method and one highly effective non-barrier method. The contraception of new female patients enrolled in the trial should have been started from 28 days prior to initiation of study treatment.

WOCBP (trial participant) 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 if their sexual partner is a man able to father a child.
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 capsules counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor or delegate.

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

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

5. ASSESSMENTS

For the assessment of primary endpoint see Section 5.2 (assessment of safety).

5.1 ASSESSMENT OF EFFICACY

This Section describes the assessment of [redacted]

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 when needed.

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), as specified in the Flow Chart.

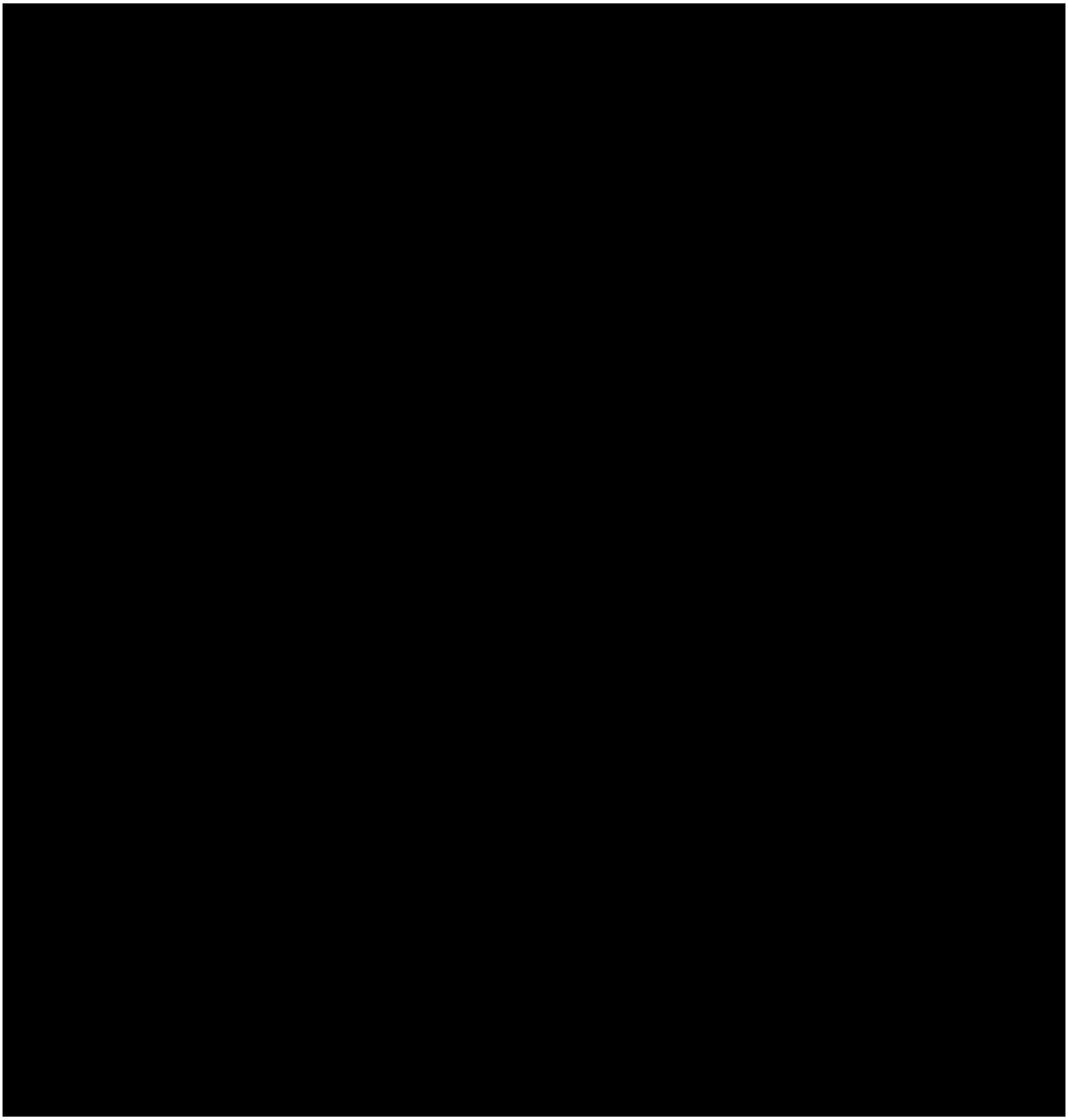
On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Smoking (if applicable) should be discouraged throughout the visit days (clinic visit) and will not be permitted in the 30-minute period prior to spirometry. Patients should 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.

[redacted]

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



5.2 ASSESSMENT OF SAFETY

This Section describes the assessment of primary [redacted] endpoints of safety.
The primary [redacted] endpoints of safety will be based on data at time points defined in Section 2.1.2 and Section 2.2.2.

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.

Measurement of height and body weight will be performed at the time points specified in the Flow Chart.
The results must be included in the source documents available at the site.

For new patients, all abnormal findings at baseline (Visit 2) will be recorded on the Baseline Condition eCRF 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 eCRF page.

5.2.1.1 Body weight

Measurement of body weight will be performed at the time points specified in the Flow Chart.

For new patients, 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. For roll-over patients, data from the 2 previous years collected in parent trial will be used.

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

These measurements will be used to assess safety and to assign the proper dose of trial medication at Visit 2 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 (see ISF for further instructions).

For new patients, 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. For roll-over patients, data from the 2 previous years collected in parent trial will be used.

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. For roll-over patients, the procedure followed to make these measurements for a given patient must be consistent with procedure followed in the parent trial as communicated to site by the sponsor.
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 eCRF.

These measurements will be used to assess safety and be periodically reviewed by the SMC.

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. The results must be included in the source documents available at the site. See also Appendix 10.5 for details.

For new patient, all abnormal findings at baseline will be recorded on the Baseline Condition eCRF 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 eCRF page.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed at scheduled visits 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.

The eGFR will be calculated based on serum creatinine according to Schwartz formula [R10-0828, R11-4789] in adolescent and according to CKD/EPI formula in adults [R12-1392] (see Appendix 10.3)

Patients do not have to be fasted for the blood sampling for the safety laboratory.

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.

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).

Overall, approximately 6.1 mL blood will be taken for standard safety laboratory tests at each scheduled visit during the trial.

Pregnancy tests
During the treatment period and the follow-up period a pregnancy test must be conducted in all female patients every 4 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. A urine dipstick pregnancy test will be conducted at the EoS/Follow-up Visit (if acceptable).

Urine dipstick pregnancy test kits will be provided locally for use between regular visits every 4 weeks.
A pregnancy test diary card will be dispensed at visits defined in the Flow Chart.
The patient/parent(s)/legal guardian will be instructed on how it should be used to support the record of the date and result of urine pregnancy test(s) between consecutive visits.
Test results must be documented in the patient's pregnancy test diary card and will be transferred to the patient's records by site staff at the next site visit. In case of positive results, procedures defined in Section 5.2.7.2.3 should be followed.

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). Safety laboratory parameters to be assessed at regular visits are listed in Table 5.2.3:1 Safety laboratory parameters to be assessed at these additional visits are listed in Table 5.2.3:2.
The samples may be collected at the office of a local doctor using preferably trial specific lab kits that will be sent to a central laboratory for analyses or may be analysed locally. These kits will be provided to patients at study visits as applicable. Around 2.5 mL will be taken at each a-Visit.

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.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.7.1 and the DILI Checklist provided in the eDC system). The amount of blood taken from the patient concerned will be increased due to these additional samplings.

The central laboratory will transfer the results of the analysis to the sponsor or delegate.

Table 5.2.3:1 Safety laboratory tests at scheduled site visits

The laboratory tests at regular site visits will include:

Functional lab group	**Test name**
Haematology	Haematocrit Haemoglobin Red blood cells (RBC) White blood cells (WBC) Platelet count Mean corpuscular volume (MCV)
Automatic WBC differential (relative and absolute)	Neutrophiles total Lymphocytes total Eosinophiles Basophiles

Functional lab group	Test name
	Monocytes Lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphonuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin Time (PT) INR
Enzymes	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (AP) Gamma glutamyl transferase (GGT) Creatine kinase (CK) Lactate dehydrogenase (LDH)
Substrates	Glucose (non fasting, V1 and V2 only) Creatinine eGFR (V1 and V2 only) Uric Acid Total bilirubin Direct bilirubin Total protein Thyroid stimulating hormone
Electrolytes	Calcium Sodium Potassium Chloride Phosphate
Serum Pregnancy test (in all female subjects) at all scheduled visits requiring blood sampling for laboratory tests and if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin
Urine Pregnancy test (dipstick) (Locally provided for use between scheduled clinic visits to assure pregnancy test every 4 weeks)	Human Chorionic Gonadotropin in the urine
Urinalysis macro panel	Semi-quantitative: Urine nitrite Urine protein Urine glucose Urine Blood Urine leukocyte esterase Urine pH

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

The laboratory tests at intermediate ‘a’-visits will include:

Functional lab group	Test name
Enzymes	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)

Functional lab group	Test name
	Alkaline phosphatase (AP) Gamma glutamyl transferase (GGT)
Substrates	Creatinine Total bilirubin Total protein
Electrolytes	Calcium Sodium Potassium Chloride Phosphate
Urinalysis	Semi quantitative: Urine nitrite Urine protein Urine glucose Urine Blood Urine leukocyte esterase Urine pH

5.2.4 Electrocardiogram

Resting 12-lead 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 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.
For new patients, 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.

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. For roll-over patients, the procedure followed to make these measurements for a given patient must be consistent with the procedure followed in the parent trial.

MRIs/x-rays of growth plates will be conducted in all patients who qualified for assignment of nintedanib treatment at Visit 2 (baseline) except in roll-over patients with closed physes at

the end of parent trial and patients that had previous MRIs or x-rays in the time window described below.

Imaging follow-ups will be conducted only in patients with open physes, at pre-defined time points until end of the study or closure of physes.

The follow-up will be planned, irrespective of scheduled visits, in order to respect the frequency of around every 12 weeks for first year and around every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial with always minimum 10 weeks (first year)/22 weeks (thereafter) and always maximum 16 weeks (first year)/28 weeks (thereafter) from previous procedure. For patients aged 19 and older, bone imaging follow-up procedures will be performed around every 48 weeks (instead of around every 24 weeks) until the end of the study or closure of the physes.

Please refer to Flow Chart footnotes for more details. Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety. Previous MRIs or x-rays of epiphyseal growth plates within respectively 12 weeks (for the first year) or 24 weeks (after the first year) prior baseline should be used at baseline for patients previously involved in InPedILD® with respectively less or more than 52 weeks in InPedILD®.

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 an external expert in radiology.
Results of central review will be reported to the investigator. In case of pathological findings/potentially pathological findings on Epiphyseal Growth Plate Results Report identified by central reviewer, the investigator should assess if these findings should be reported (as AE/AESI) or not (see Section 5.2.7.1.4.).
In addition, all MRI/x-ray assessments and height measurements (see Section 5.2.1.2) will be periodically reported to the SMC.

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 to assess the potential severe/irreversible effects of nintedanib on teeth in the study population:

Dental examination will be conducted in all patients who qualified for assignment of nintedanib treatment at Visit 2 (baseline). Follow-up will be conducted at predefined time points. Dental examination follow-ups will be planned, irrespective of scheduled visits, in order to respect the frequency of around every 12 weeks for first year and around every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial with always maximum 16 weeks (first year)/28 weeks (thereafter) from previous procedure. Please refer to Flow Chart footnotes for more details. Timepoints may be adapted on a case-

by-case basis after discussion with the sponsor if appropriate for patient's safety. Previous dental examination within 12 weeks prior baseline may be used at baseline for patients previously involved in InPedILD®.

Dental imaging will be conducted in all patients who qualified for assignment of nintedanib treatment at Visit 2 (baseline) and do not have previous panoramic x-ray in the time window described below available. Follow-up will be conducted at predefined time points until the end of the study. Dental imaging follow-ups will be planned, irrespective of scheduled visits, in order to respect the frequency of around every 24 weeks for first year and around every 48 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial with always minimum 22 weeks (first year)/46 weeks (thereafter) and always maximum 28 weeks (first year)/52 weeks (thereafter) from previous procedure. Please refer to Flow Chart footnotes for more details. Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety. Previous panoramic x-ray within 24 weeks prior baseline may be used at baseline for patients previously involved in InPedILD®.

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.
Results of central review will be reported to the investigator. In case of pathological findings/potentially pathological findings identified by central reviewer, the investigator should consult immediately the local dentist, to confirm if these findings should be reported (as AE/AESI) or not (see Section 5.2.7.1.4.).

Dental examination and imaging will be periodically reported to the SMC.

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 considered related or not.

The following should also be recorded as an AE in the eCRF 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 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. However, if these abnormalities are Adverse events from the parent trial in patients that have been rolled over and are still ongoing at Visit 1, then they should not be recorded as baseline conditions but as ongoing Adverse Events.

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 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 in Section 5.2.7.2.
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 be followed up according to the "DILI checklist" provided in the eDC system.

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.

In addition, the intensity (severity) of diarrhoea adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 on an additional diarrhoea adverse events eCRF [R18-1357]. See Table 5.2.7.1.5: 1. below.

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 the relationship between the adverse event and the BI investigational compound, 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 trial 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 trial 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.
- There is an 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 eCRF(s) by the investigator:

From signing the informed consent onwards until the individual patient's end of trial (= the End of Study (EoS) visit): all AEs (serious and non-serious) and all AESIs.

For roll-over patients, any (S)AE that occurred after start of treatment in the parent trial and is continuing up to Visit 1 of this extension trial, will be recorded as (S)AEs at Visit 1 of this trial with the same information as it was recorded in the parent trial. If this ongoing AE is an SAE, then the follow-up report will still be sent on the parent trial SAE form, no new SAE form is to be completed for the extension trial.

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 drug related SAEs and trial drug 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 (Section 5.2.7.2.2.), but not on the eCRF.

Vital Status Data Collection
Patients who discontinue trial treatment prematurely, who 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 any occurrence of cancer, report all deaths / fatal AEs regardless of relationship, and trial drug related SAEs and trial drug 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 to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific process will be specified 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 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

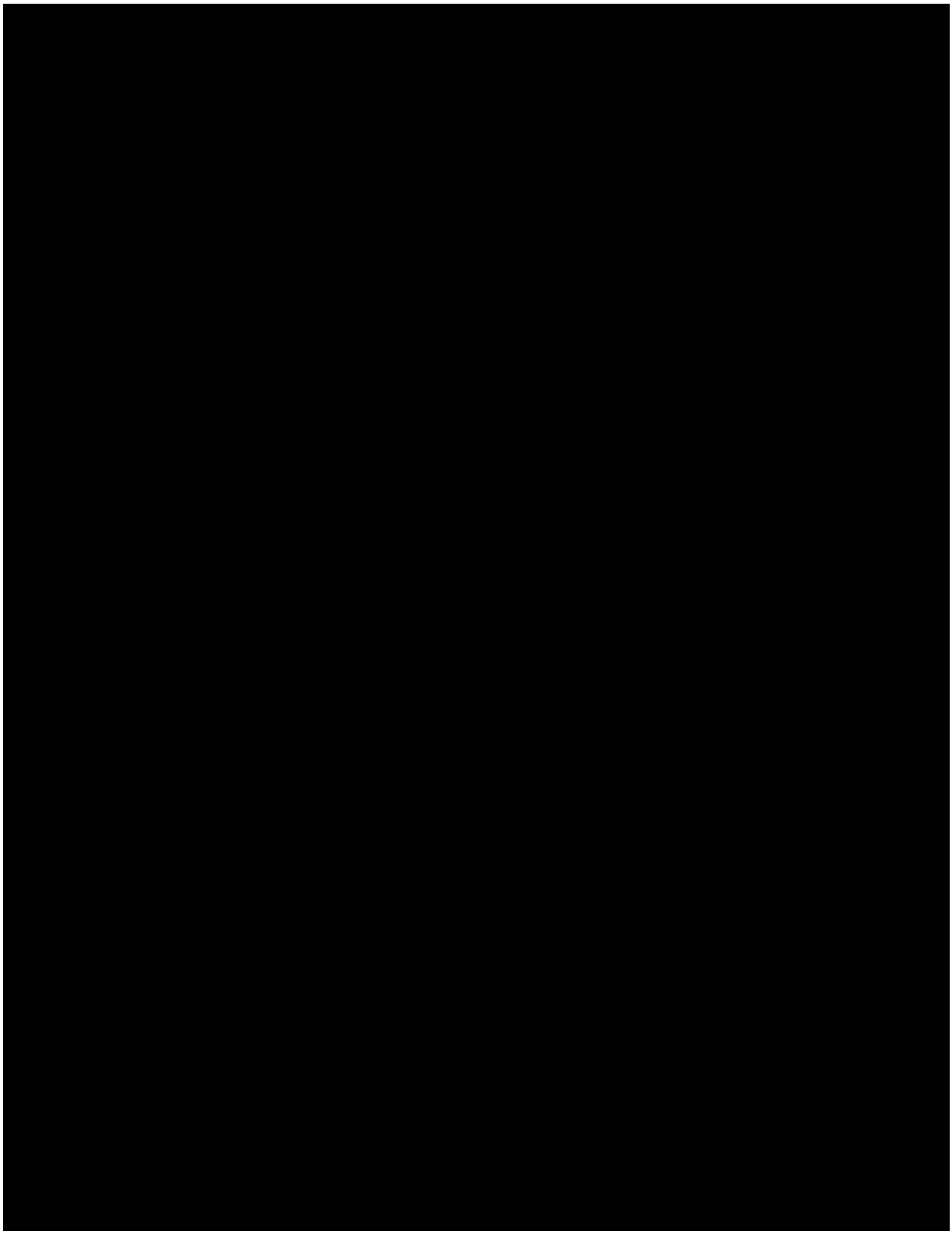
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring 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 Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (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 Studies 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

- An external expert in radiology will review all MRI/radiological assessments (bone imaging). Additionally, images of a particular patient may be reviewed by other radiology or clinical experts selected by the sponsor for consultancy, if judged needed by the sponsor to assess safety of this particular patient or to support overall safety assessment.
- A blinded external expert in paediatric dentistry will review all panoramic x-rays (dental imaging). Additionally, images of a particular patient may be reviewed by other external dentist/expert in paediatric dentistry selected by the sponsor for consultancy, if judged needed by sponsor to assess safety of this particular patient or to support overall safety assessment.
- An independent 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. In parallel, the Adjudication Committee/a member of the Adjudication Committee will review all dental findings of stunted growth of the dental root identified by central review to assess them to either pathological finding /stunted growth or not. Certain further dental findings on dental imaging may potentially be assessed if defined in the Adjudication Charter (dental imaging from 1199-0337 study may be included in this assessment process).

- 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’.



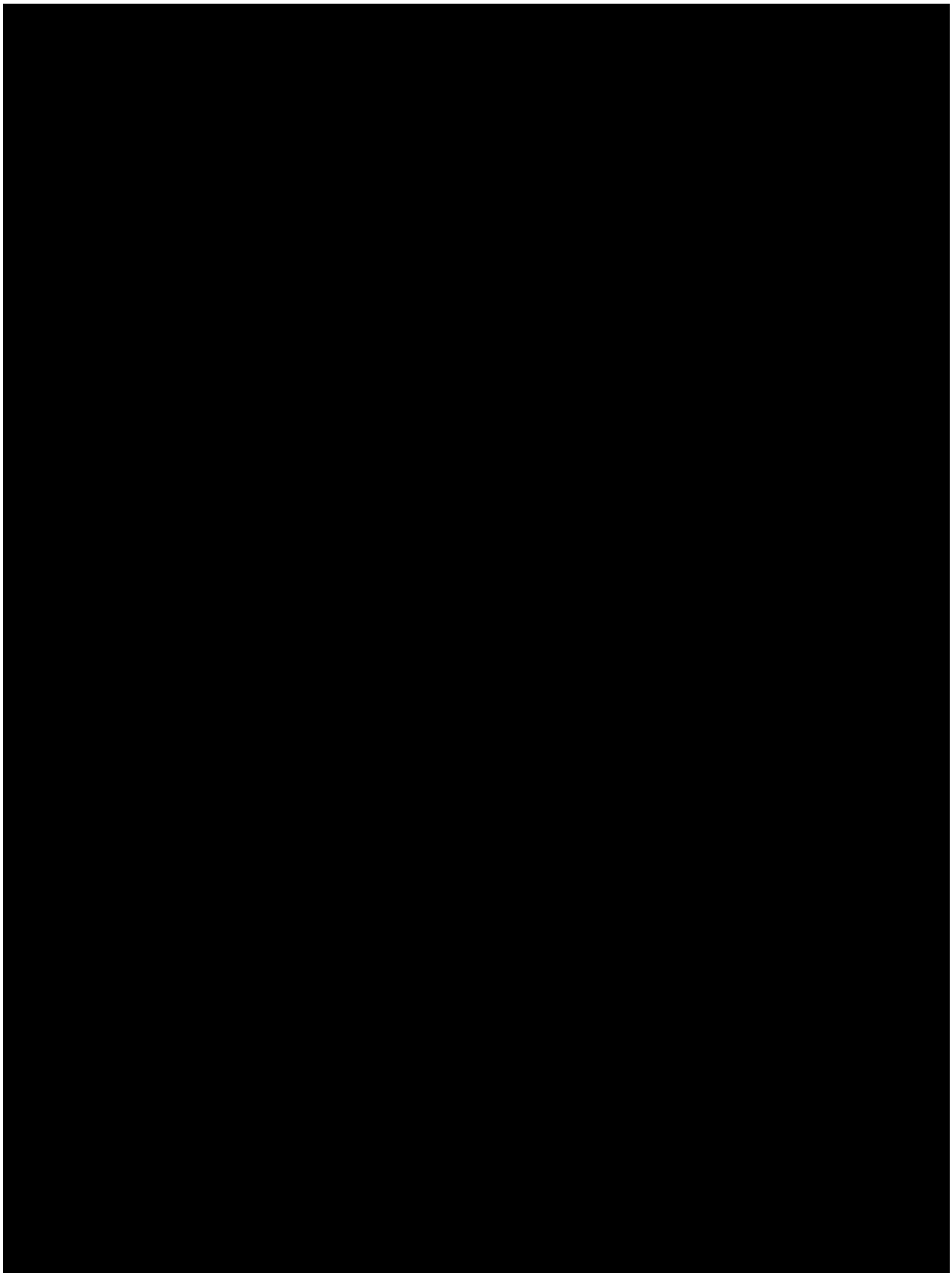
[redacted]

5.5 BIOBANKING

n.a.

5.6 OTHER ASSESSMENTS

[redacted]



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 new patients.

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.

For new patients, D_{LCO} will be measured at Visit 2 and corrected for haemoglobin (Hb) measured at Visit 1 (see Appendix 10.4 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.

[redacted]

Physician reported Fan severity score [R09-5337] at Visit 2 will be used to determine eligibility of new patient. [redacted]. For instructions on how to assign the severity-of-illness score see Appendix 10.2

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.

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 new 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 measurements and measurements outlined in Section 5.3 are generally used as measurements to assess drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All study visits should be scheduled as defined in the Flow Chart. Some flexibility is allowed by time windows specified in order to accommodate scheduling problems.
All efforts should be made to perform all visits as requested. If a delay is observed for a particular visit, subsequent visits should follow the original planned visit schedule (calculated from Visit 2).
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.
All deviations from the planned visit schedule will be documented.

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.
- [redacted]
- Spirometric measurements should always be conducted at the same time (+/- 90 min) with reference to baseline measurement (Visit 2).

The trial will run until all patients have stopped treatment, which is when, nintedanib is available outside the clinical trial or alternative treatment options become available or a stopping criterion is met according to Section 3.3.4

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent/assent of the patient/parent(s)/legal guardian, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be 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 patient/parent(s)/legal guardian. The implementation of these measures will depend on consent from the patient/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

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 pediatric patient during the visit taking in account its age-appropriate needs.

Study procedures and assessments to be performed at each visit are listed in the Flow Chart.
Explanations of procedures and assessments are given in Section 5.
Additional details regarding visit procedures and assessments are provided below.

6.2.1 Screening and run-in period(s)

For new patients,

Before or at the latest at Visit 1

- Informed consent (and assent where applicable) will be obtained before any procedure related to the study, including HRCT transfer to central review.
- Upon obtaining informed consent, the investigator will register the patient's Screening transaction in the IRT system, and the patient will receive a patient number and trial identification card.
- A preliminary check of in-/exclusion criteria is recommended at time of informed consent to avoid unnecessary wash-out procedures in non-eligible patients.
- 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), an HRCT can be performed for the purposes of participation in the trial provided the patient meets eligibility criteria that can be assessed at that time point.
- 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
- After giving informed consent, the patient will enter in the screening period. Patient/parent(s)/legal guardian will be instructed on procedures to be followed until the next study visit. The Visit 1 should take place within 28 days prior to Visit 2. Results of all study procedures and assessments in determining patient's eligibility must be available prior to Visit 2.

Visit 1 (Screening)

Information to be collected during screening period:

- Demographic will be recorded. This includes age on the day of informed consent (in years and month)
- Sex (male, female in order to describe the subject's sex at birth),
- Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed unless not acceptable according to local regulations.
- Baseline Conditions/Medical History:
  - Medical history including pre-existing conditions (including [redacted] if applicable) will be recorded.
  - Concomitant therapy including previous medications [redacted] 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.
- [redacted].
- FVC measurement will be conducted with the spirometer provided by the sponsor, according to procedures defined (see ISF for details).
- Prior to blood draw a pre-assessment of all in-/exclusion criteria is highly recommended to avoid unnecessary blood draws.
- 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).

- 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, an HRCT will be done and sent to central review by site personnel (if not done before).

- If the patient qualifies to enter the screening period, Visit 2 will be scheduled; patient/parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.

- If a patient results in a screen failure the patient must be registered as a screen failure in IRT system. Patient rescreening is possible later. At due time a new informed consent/assent will be collected. Rescreening transaction must be registered in the IRT system. A new patient number will be provided which will be linked to the previous patient number in the IRT system and patient will complete all study procedures according to Flow Chart. Re-screening of a previously screen failed patient will be permitted once.

For roll-over patients,

- Informed consent (and assent where applicable) must be obtained before any procedure related to the 1199-0378 trial. After giving informed consent, the patient is considered to have started the screening process and is assigned a unique patient number in the IRT system. A trial identification card is provided.

- Visit 1 and Visit 2 should be conducted the same day and should, if possible, occur the same day as the EoT Visit of the parent trial to avoid any treatment interruption. In this case, informed consent/assent must be obtained at the latest, at the beginning of 1199-0337 EoT visit before any procedure (in particular, before any blood sample collection). Assessments conducted as part of EoT of the InPedILD® trial do not need to be repeated if they are performed the same day. In case it is not possible to perform Visit 1 on the same day as the EoT Visit of InPedILD®, the maximum time allowed between EoT of parent trial and Visit 1 of this trial will be 8 weeks. (for details of combined Visit 1/Visit 2, please refer to Section 6.2.2)

- [redacted]

6.2.2 Treatment period(s)

Visit 2:
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 assignment of study treatment. The screening phase (from informed consent until Visit 2) must be no longer than 12 weeks.

Detailed procedures and assessment to be performed at Visit 2 are described in Flow Chart and Section 5.

Visit 2 for new patients

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 eGFR measurement have been provided and are available at the site.

Observations and procedures
- [redacted]
- [redacted]

- Adverse events, [redacted], concomitant therapy [redacted] 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 entered timely 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.
- [redacted]
- FVC measurement will be conducted according to procedures defined (see ISF for details).
- DLCO measurement will be conducted after FVC measurement and patient's rest. DLCO will be corrected for haemoglobin (Hb) measured at Visit 1 (see Section 5.6.4 for details).
- 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.
- [redacted].
- 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, treatment assignments will be performed by using the IRT system.
- The assigned trial medication will be administered at the site.
- Medication wallets will be dispensed, patient/parent(s)/legal guardian will be properly instructed about how and when the study medication should be taken until the next visit. The patient/parent(s)/legal guardian will be properly instructed to contact the site in case of adverse events (details given in the informed consent and assent where applicable).
- [redacted]
- The next visit will be scheduled; patient/ parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.

Procedures to be conducted in all eligible patients, if possible, on the day of the visit, or if not, to be done in the 2 weeks immediately after the visit (please refer to the image acquisition guideline available in the ISF for details).

- An MRI of epiphyseal growth plates will be conducted 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 according to protocol requirements (see Section 5.2.6) and evaluated at site.
- Dental imaging will be conducted 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, by the end of Visit 2, the patient does not qualify for assignment of study treatment, screening failure will be notified via IRT.

Visit 1/Visit 2 for roll-over patients

Assessments conducted as part of EoT of the InPedILD® trial do not need to be repeated if they are performed the same day in particular:

- Physical examination including vital signs, weight, height (standing and sitting), and leg length
- 12-lead ECG
- [redacted]
- FVC measurement
- Blood and urine samples for safety laboratory tests, [redacted] (and pregnancy test on serum in female patients only)
- 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.

Prior to additional blood draw, the assessment of all in-/exclusion criteria is highly recommended to avoid unnecessary blood draw.

- An additional blood sample to check safety parameter(s) [redacted] for the 1199-0378 study may be collected at the same time as blood and urine samples for EoT of 1199-0337.

Information to be collected at this visit:

- Demographic will be recorded. This includes age on the day of informed consent (in years and month), sex (male, female in order to describe the subject's sex at birth),
- Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed, y unless not acceptable according to local regulations.
- Baseline Conditions/Medical History:
  - Medical history including pre-existing conditions ([redacted]) will be recorded.
  - Concomitant therapy including previous medications [redacted] will be recorded.
  - Any adverse events (since consent, if applicable) will be recorded. If this AE is an ongoing AE from parent trial, then it will be recorded as AE with same information than in the parent trial

Other observations and procedures

- [redacted]
- If a patient is eligible for the trial, treatment assignments will be performed by using the IRT system.

- The first dose of assigned trial medication will be administered at the site.
- Medication wallets will be dispensed, patient/ parent(s)/legal guardian will be properly instructed about how and when the study medication should be taken until the next visit. The patient/parent(s)/legal guardian will be properly instructed to contact the site in case of adverse events (details given in the informed consent and assent where applicable).
- [redacted] will be dispensed; the patient/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/parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.

Procedures to be conducted if possible, in all eligible patients, on the day of the visit, or if not, to be done in the 2 weeks immediately after the visit (please refer to the image acquisition guideline available in the ISF for details).

- Bone imaging: Previous MRIs or x-rays of epiphyseal growth plates within 12 weeks prior baseline should be used as baseline for roll-over patients with less than 52 weeks in InPedILD®. Previous MRIs or x-rays of epiphyseal growth plates within 24 weeks prior Visit 2 should be used as baseline for roll-over patients with more than 52 weeks in InPedILD®. If a previous MRI or x-ray as outlined above, is not available, imaging of epiphyseal growth plates should be conducted according to protocol requirements (see Section 5.2.5). If MRI cannot be performed, an x-ray will be conducted. Not applicable for patients with closed physes at the end of InPedILD®.
- Dental examination: Previous panoramic x-ray within 12 weeks prior Visit 2 should be used as baseline. If a previous dental examination as outlined above is not available, a dental examination will be conducted according to protocol requirements (see Section 5.2.6) and evaluated at site.
- Dental imaging: Previous panoramic x-ray within 24 weeks prior Visit 2 should be used as baseline. If a dental imaging is not available as outlined above, a dental imaging will be conducted 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.

Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, X (treatment period)

Additional clinic visits will be scheduled on regular basis from Visit 2 until End of Treatment (EOT) visit. Detailed procedures and assessment to be performed at each Visit are described in Flow Chart and Section 5.
As the treatment duration for each patient will be variable, some visits may not apply (to some new patients and to some patients aged 21)

For roll-over patients with 26 weeks or more in InPedILD®, Visit 3 is not needed. This additional visit is scheduled after 2 weeks of treatment to assure close monitoring of new patients and roll-over patients with less than 26 weeks in InPedILD®, during the first month of study.

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

- [redacted]

- FVC measurements at all visits should be performed approximately at the same time of the day to reference time point at Visit 2.

Observations and procedures:

[redacted]

Observations and procedures [redacted]:

[redacted]

Other observations and procedures:

- 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 and confirm that since the last scheduled visit at the site the pregnancy test has been repeated every 4 weeks until the current visit. If not confirmed, the investigator will re-instruct the patient/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 (applicable for female patients only, all scheduled visits after Visit 3).
- Adverse events, [redacted], concomitant therapy [redacted] 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 3; leg length planned at Visit4, Visit 5, Visit 6, Visit 7, Visit 9, Visit 11, Visit 13, Visit 15 and every 24 weeks thereafter, until the end of the study); 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 5, Visit 7, Visit 9, Visit 11, Visit 13, Visit 15 and every 24 weeks thereafter, until the end of the study).

- [redacted]
- FVC measurement will be conducted according to procedures defined (see ISF for details).
- [redacted]
- [redacted]
- 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).
- [redacted]; the patient/parent(s)/legal guardian will be instructed on how it should be completed in the 3 days before the next visit (Visit 4 only).
- A pregnancy test diary card will be dispensed; the patient/parent(s)/legal guardian will be instructed on how it should be used to support the record of the date and result of urine pregnancy test(s) between consecutive visits (applicable for female patients only, all scheduled visits after Visit 3).
- The next visit will be scheduled; patient/parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.

Procedures to be conducted at predefined time points, irrespective of scheduled visits, according to time window defined in the Flow Chart. If it is not possible to conduct the follow-up at the predefined time points, please refer also to footnotes 21, 22, and 23 in the Flow Chart.

- Follow-up bone imaging (MRIs or x-rays if baseline MRI was not possible) will be planned, in order to follow the frequency of around every 12 weeks for first year and around every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial:

  •**For new patients,** imaging follow-up will be conducted, if applicable, at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks, 128 weeks, 156 weeks, and every 24 weeks thereafter until the end of the study or closure of the physes.

  •**For roll-over patients**, imaging follow-up will be conducted around every 12 weeks in the following year after the MRI/x-ray considered as baseline for parent trial (when applicable) and around 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.

  • For patients aged 19 and older, bone imaging follow-up procedures will be performed around every 48 weeks (instead of around every 24 weeks) until the end of the study or closure of the physes.

- Follow-up dental examination will be planned in order to follow the frequency of around every 12 weeks for first year and around every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial:
  - **For new patients,** follow-up will be conducted, if applicable, at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks, 128 weeks, 156 weeks, and every 24 weeks thereafter until the end of the study.
  - **For roll-over patients**, follow-up will be conducted around every 12 weeks in the following year after the dental examination considered as baseline in parent trial (when applicable) and around every 24 weeks thereafter until the end of the study.
- Follow-up dental imaging will be planned in order to follow the frequency of around every 24 weeks for first year and around every 48 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial:
  - **For new patients,** follow-up will be conducted, if applicable, at 24 weeks, 52 weeks,104 weeks, 156 weeks, and every 48 weeks thereafter until the end of the study.
  - **For roll-over patients**, follow-up will be conducted, irrespective of scheduled visits, around every 24 weeks in the following year after the dental imaging considered as baseline for parent trial (when applicable) and around every 48 weeks thereafter until the end of the study.

  Dental imaging will be sent to central evaluation by paediatric dentistry expert on a timely manner.

[redacted]

Dose reduction visit / dose increase visit/ Change of capsule size visit

If a patient experiences a drug related AE, the dose can be reduced via IRT and the dose can be increased to the original dose via IRT after recovery as described in Section 4.1.2.
If a patient, assigned to 150 mg or 100 mg bid, is not able to swallow the 150 mg strength or the 100 mg strength capsule, the patient will have the possibility to take the 25 mg strength capsules (6 or 4 capsules per dose, respectively).

If the dose change or change of capsule size does not occur in concomitance to a scheduled visit, the patient will attend an unscheduled visit at the site for this dose reduction or dose increase or capsule change.
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, [redacted], concomitant therapy [redacted] 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).

In case the start/end of an AE requires a dose reduction/increase without the need of a change in capsule size and without requiring a meeting with the investigator in person, the unscheduled visit for the patient can be replaced by a phone call. The investigator will register the phone call in IRT as an unscheduled visit and register the dose reduction/increase on the respective page in the eCRF.

Intermediate 'a-Visits'
Intermediate lab tests ("a"-Visits) for safety monitoring may be conducted between scheduled visits, 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 may give the patient/parent(s)/legal guardian 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 (preferable option) or samples may be analysed locally.

Intermediate pregnancy tests
During the treatment period and the follow-up period a pregnancy test must be conducted in all female patients every 4 weeks.
Urine dipstick pregnancy test kits will be provided locally for use between visits when visit intervals are > 4 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.

Treatment period duration
Treatment duration for each patient will be variable.
Roll-over patients will be requested to stay in the trial for at least 156 weeks (until Visit 15). At week 156, roll-over patients who can be treated with nintedanib or alternative treatment options outside the clinical trial will have their EoT Visit. The remaining roll-over patients will continue in the trial until nintedanib or alternative treatment options become available to them outside the clinical trial.

Trial treatment will be stopped prematurely if a reason for withdrawal is met (refer to Section 3.3.4).

After week 156, if reason for study treatment discontinuation is that nintedanib or alternative treatment options become available for patient outside the clinical trial, then the patient will not be considered as early discontinued for treatment.

New patients will stay in the trial until the overall end of the trial (with expected minimum treatment duration of 76 weeks), then patients will perform the EoT Visit.

End of Treatment Visit

If a patient discontinues the study during a scheduled treatment visit, then the scheduled visit will be replaced by the EoT visit. As consequence, roll-over patients that discontinue trial treatment at week 156 should perform EoT visit instead of Visit 15.

Observations and procedures:

- [redacted]
- Compliance will be checked, and drug accountability will be completed.
- The site personnel will check the pregnancy test diary card and confirm that since the last scheduled visit at the site the pregnancy test has been repeated every 4 weeks until the current visit. Refer to Section 5.2.7.2.3 for detailed information on event reporting in case of pregnancy (applicable for female patients only).
- Adverse events, [redacted], concomitant therapy [redacted] 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; 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.
- [redacted]
- FVC measurement will be conducted according to procedures defined (see ISF for details).
- [redacted]
- 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 applicable and if not collected before.
- A pregnancy test diary card will be dispensed; the patient/parent(s)/legal guardian will be instructed on how it should be used to support the record of the date and result of urine pregnancy test(s) between consecutive visits (applicable for female patients only).
- The EoT visit will be registered in the IRT system and dispensed, returned wallets will be collected as instructed (see ISF for details).
- The next visit will be scheduled; patient/parent(s)/legal guardian will be instructed on procedures to be followed until the next visit.

Procedures to be conducted if possible, on the day of the visit, or if not, to be done in the week immediately before or after 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. The MRI/x-ray should not be repeated if the last MRI/x-ray was conducted within 24 weeks.

- Follow-up dental examination will be conducted in all patients at EoT. The dental examination will not be repeated if the last examination was conducted within 12 weeks.
- Follow-up dental imaging will be conducted in all patients at EoT. The dental imaging will not be repeated if the last examination was conducted within 24 weeks.

Exception: patients aged 21 years must complete the trial before their 22nd birthday.
The EoT visit followed by EoS visit must be performed before the 22nd birthday.

Patients who prematurely discontinued trial medication
Patients who discontinued trial treatment prematurely will undergo the EoT visit as soon as possible.

Roll-over patients who discontinued trial treatment prematurely before week156, patient will be asked to remain in the study and to return to remaining scheduled visits until the initial planned week 156 (Visit 15)
New patients who discontinued treatment prematurely will be asked to remain in the study and to return to remaining scheduled visits until the overall end of trial.

At remaining scheduled visits, all procedures and assessments planned to be done under treatment need to be followed by the patient [redacted] and IRT call/notification.
The first visit after the EoT will be skipped if the EoT Visit occurs within 4 weeks prior to the scheduled visit but if MRI and/or dental examinations were planned at this visit, then they should be performed as planned. Only one additional regular follow-up for bone imaging and for dental imaging procedures will be needed after the EOT visit if there is no pathological finding. If there is a pathological finding, follow-up procedures will be conducted on individual basis upon discussion with the sponsor and with the investigator. Follow –up procedures for clinical dental examination will be conducted as initially planned by the protocol. Urine pregnancy tests at home (for female patients) are only required to be continued every 4 weeks for the 3 months after last trial drug intake.
The last visit to be performed by prematurely discontinued roll-over patients will be the Visit 15 including trial completion and the last visit to be performed by new patients prematurely discontinued will be EoS including trial completion.

If patients are not able to complete the remaining scheduled visits, a follow-up (FU) visit should be planned for 28 days after EoT. In addition, every attempt will be made to get information on vital status, when applicable, at 24 weeks, 52 weeks, 76 weeks and 104 weeks, 128 weeks, 156 weeks, and for new patients at EoS.

Exception: patients aged 21 years must complete the trial before their 22nd birthday.
Remaining scheduled visits or vital status will be replaced by the EoS visit which must be performed the 22nd birthday.

Additionally, for treatment discontinued patients, if it is intended by the patient to use commercial nintedanib after trial treatment discontinuation, the patient should directly undergo the EoS visit 28 days after the EOT visit.

Follow-up visit:
F-up visit should be conducted 28 days (+7 days) after the EoT visit for all discontinued patients who are not able to complete the remaining visits off-treatment or who accepted the vital status collection
If the EoT visit has been delayed and has been done 28 days or more after the treatment discontinuation, the follow-up visit can be skipped

Observations and procedures to be performed are listed in the Flow Chart.

6.2.3 Follow-up period and trial completion

End of Study visit
EoS visit should be conducted 28 days (+7 days) after the EoT visit for patients who have completed the trial on treatment as planned.
In exceptional cases, when the patient is not able to come at site for medical reason, the EoS visit can be replaced by a phone call.
If the EoT visit has been delayed and has been done 28 days or more after the treatment discontinuation, the EoS visit can be skipped.

The EoS should be conducted at week 156 for prematurely discontinued roll-over patients who were able to complete the remaining visits off-treatment until week 156 and at the overall end of the trial for new patients who prematurely discontinued trial treatment and were able to stay in the trial until the overall end of trial.

Observations and procedures:
- Adverse events, [redacted], concomitant therapy [redacted] 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 EoS in case of clinically relevant changes at EoT.
- [redacted]
- Pregnancy test on urines will be conducted in female patients only. Test results will be documented in the patient's records.

If needed in the opinion of the investigator, after the EoS visit, additional visits may be scheduled for continued safety monitoring.

Abnormal assessments or lab values judged clinically relevant by the investigator will be monitored until they returned to a medically acceptable level.

Trial completion

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

- At the end of the EoS Visit for patients who have completed the trial on treatment as planned (including patients aged 21).
- At week 156, for roll-over patients who prematurely discontinued trial treatment before Visit 15 and were able to stay in the trial until week 156.
- At the overall end of the trial for new patients who prematurely discontinued trial treatment and were able to stay in the trial until the overall end of trial.
- At F-up/EoS visit, for roll-over patients who prematurely discontinued trial treatment before Visit 15 and were not able to stay in the trial until week 156 and for new patients who prematurely discontinued trial treatment and were not able to stay in the trial until the overall end of trial.
- At last contact, for other cases.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

As the main objective of this extension trial is to study long-term tolerability and safety, only descriptive statistics will be used. Some limitations due to the nature of the extension trial should be considered when interpreting the data (bias in the selection of the population, no comparative arm). All endpoints are considered exploratory only.

This statistical paragraph deals with the analyses to be performed on the extension trial only.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory testing is performed and hence no null and alternative hypotheses are defined.

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 have received and taken at least one dose of open-label trial medication.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be documented in the DV domain template including protocol deviations relevant to the [redacted]. IPDs will be identified no later than in the final Report Planning Meeting, and the iPD categories will be updated as needed.

Patients will be analysed depending if and when they rolled-over from the parent trial (Group 1: New Patients [including patients who prematurely discontinued treatment permanently in 1199-0337, and completed patients from the parent trial not able to roll over into the extension trial within 12 weeks following their End of Treatment visit in the parent trial] and patients from 1199-0337 placebo arm Part A –, Group 2: patients from 1199-0337 Part B and from 1199-0337 nintedanib arm Part A) and overall.

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

Endpoints will be analysed for those patients where respective data is collected.

Further details will be specified in the TSAP.

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are:

- Treatment discontinuation

The strategies for handling intercurrent events in this trial are as follows:

While-on-Treatment: This is the effect of treatment while patients take it. Intercurrent events will be handled by default using the while-on-treatment approach as defined in ICH E9(R1), with the treatment period defined as the period from first trial drug administration to the end of the residual effect period following last administration. Any changes to background therapy or temporary discontinuations of trial drug will be considered part of the treatment regimen being assessed.

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

7.2.3 Primary objective analyses

The primary endpoint listed in Section 2.1.2 will be derived according to BI standards. The primary analysis refers to the number of patients with any treatment-emergent adverse event reported during the trial, i.e. all adverse events occurring between start of treatment and end of the REP. The analysis will be based on the TS and will be descriptive in nature.

As the primary objective of the study is to assess the tolerability and safety of nintedanib, please refer to Section 7.2.6.

7.2.3.1 Sensitivity Analyses

No sensitivity analysis planned.

7.2.3.2 Subgroup Analyses

Subgroup analyses will be specified in the TSAP.

7.2.3.3 Supplementary Analyses

No supplementary analysis planned.

7.2.4 Secondary objective analyses

Not applicable.

[redacted]

7.2.6 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'. The frequency of patients with AEs as well as incidence rates per 100 patient years will be presented.

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. Patient 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.

Further details will be provided in the TSAP.

7.2.8 Interim Analyses

One interim analysis is planned after 1 year, i.e. after all roll-over patients completed the 52 weeks visit or prematurely discontinued from the trial. Additional interim analyses could be performed upon request from Health Authorities or for publication purposes. All the previously mentioned analyses may be presented at each interim analysis. Further details will be provided in the TSAP.

A Safety Monitoring Committee (SMC) will be in place with tasks as described in Section 8.7.

[redacted]

7.3 HANDLING OF MISSING DATA

Missing or incomplete AE dates will be imputed according to BI rules. No imputation is planned for other safety criteria.

Missing or incomplete data for [redacted] will be handled using standard survival analysis techniques (i.e. censoring).

In the analysis of continuous endpoints, missing data will not be imputed.

[redacted]

Further details will be provided in the TSAP.

7.4 RANDOMISATION

Not applicable in this open label study.

7.5 DETERMINATION OF SAMPLE SIZE

Not applicable as this is an open label trial to collect information on long-term tolerability and safety from patients rolling over from InPedILD® and newly identified patients with high unmet medical need. There will be two cohort of patients included in this trial:

1. Patients who have completed and did not prematurely discontinue trial medication in the InPedILD® study, who fulfil the eligibility in this trial and are willing to participate.
2. Newly identified children and adolescents with clinically significant fibrosing ILDs who meet eligibility criteria of this trial.

It is expected that at least 30 patients will roll-over from trial InPedILD® and that approximately 20 to 30 newly identified patients with clinically significant fibrosing ILDs will enter treatment.

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

The trial will be carried out in accordance with the Medical Device Regulation (EU) 2017 / 745 and the harmonised standards for Medical Devices (ISO 14155, current version).

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 or delegate 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 parent(s)/legal guardian (and written informed assent must be obtained from the patient, where applicable) or when applicable by patient (or the patient’s legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country.
For adolescents, where applicable, the patient will be provided with an age-adapted information sheet where his/her assent will be collected according to the regulatory and legal requirements of the participating country.

Each signature must be personally dated by each signatory and the informed consent/assent and any additional patient/parent(s)/legal guardian-information form retained by the

investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.
The patient /patient's parent(s)/legal guardian must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent/assent of the patient/patient's parent(s)/legal guardian own free will with the informed consent form /assent form after confirming that the patient /patient's parent(s)/legal guardian understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form/assent form when 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 form / assent form.
The refusal of an adolescent to participate must be accepted independently of the consent of his/her parent(s)/legal guardian.
For patients who may legally consent during the trial participation (turning to the age of legal consent in the participating country), written informed consent must be obtained to confirm the patient's willingness to pursue trial participation.

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 should be properly documented in the source documentation. 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 or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, 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 documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. 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 trial).
Data reported on the eCRF 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 eCRF
- 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, [redacted], 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 and to any other radiology/clinical experts or to any other external dentist/experts in pediatric dentistry selected by the sponsor for consultancy. 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 the eCRF, data must be derived from source documents, 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/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 (if applicable)
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome 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.

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 [redacted]
- laboratory print-outs
- biopsy slides including any reading by the pathology expert (if applicable)
- originals or copies of HRCT scans including any reading by the thoracic radiology expert (if applicable)
- 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 (if applicable)
- 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 eCRF 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 eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, 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 site(s):
The trial site(s) 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, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- [redacted]
- 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
- [redacted]
- [redacted]

- Samples and / or data may be transferred to third parties and other countries as specified in 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 consent.
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 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 one year 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 to 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 and adolescents. Relevant documentation on all participating (Principal) Investigators and other important study personnel, including their curricula vitae, will be filed in Investigator Site File (ISF). The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

A blinded external expert in thoracic radiology will review HRCT scans from new patients 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 from new patients 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 external expert and images will be provided to the SMC for the evaluation of potential effects on bone development. Additionally, images of a particular patient may be reviewed by other radiology or clinical experts selected by the sponsor for consultancy, if judged needed by sponsor to assess safety of this particular patient or to support overall safety assessment. Tasks and responsibilities are defined in a contract for each expert.

A blinded external expert in paediatric dentistry will review all panoramic x-rays. Review by external expert and panoramic x-rays will be provided to the SMC for the evaluation of potential effects on teeth. Additionally, images of a particular patient may be reviewed by a second paediatric dentistry for consultancy, if judged needed by the sponsor to assess safety of this particular patient or to support overall safety assessment. Tasks and responsibilities are defined in a contract for each expert.

A SMC composed of external experts independent from the trial and selected BI non-trial team members will be established to review [redacted] 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 dental 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.

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 new patients evaluated for study participation at Visit 1. Members of the committee will be blinded to patient screening outcome. 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.

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). In parallel, the Adjudication Committee/a member of the Adjudication Committee will review all dental findings of stunted growth of the dental root identified by central review to assess them to either pathological finding /stunted growth or not. Certain further dental findings may potentially be assessed if defined in the Adjudication Charter (dental imaging from 1199-0337 study may be included in this assessment process).

A steering committee will provide scientific advice on the clinical development program of nintedanib in the pediatric population. Tasks and responsibilities are defined in a contract.

BI has appointed a Clinical Trial 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.

In the participating countries the trial 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) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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, central Spirometry Manual, Central Imaging Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 [redacted]

[redacted]

10.2 FAN SEVERITY SCORE

The severity-of-illness score assigned by the investigator will be based on information in the patient records at the time of evaluation [R09-5337]. Refer to Table 10.2:1 for details.

Table 10.2:1 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

10.3 ESTIMATED GLOMERULAR FILTRATION RATE

- Calculation of eGFR according to Schwartz Formula in adolescents 13-17 years old [R10-0828]

Conventional:

- in adolescent males k=0.70:

eGFR (mL/min./1.73m^2) = height (cm) x 0.70 / serum creatinine (mg/dL)

- in adolescent females k=0.55:

eGFR (mL/min./1.73m^2) = height (cm) x 0.55 / serum creatinine (mg/dL)

SI:

- in adolescent males k=0.70:

eGFR (mL/min./1.73m^2) = height (cm) x 0.70 / (serum creatinine (µmol/L) x 0.01131)

- in adolescent females k=0.55:

eGFR (mL/min./1.73m^2) = height (cm) x 0.55 / (serum creatinine (µmol/L) x 0.01131)

Calculation of eGFR according to Schwartz Formula in children 2-12 years of age [R11-4789]:

Conventional:

- in children 2-12 years of age k=0.41:

eGFR (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:

eGFR (mL/min/1.73m^2) = height (cm) x 0.41 / (serum creatinine (µmol/L) x 0.01131)

Calculation of eGFR according to CKD/EPI formula in adults [R12-1392]**:**

Conventional:

eGFR (mL/min/1.73m^2) = 141 x min(SCr /κ, 1)α x max(SCr /κ, 1)$^{-1.209}$ x 0.993^{Age} x1.018 [if female] x 1.159 [if Black]

SCr = standardized serum creatinine (mg/dL)
κ = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of SCr/κ or 1
max = indicates the maximum of SCr/κ or 1
age = years

SI:

eGFR (mL/min/1.73m^2) = 141 x min(SCr /κ, 1)α x max(SCr /κ, 1)$^{-1.209}$ x 0.993^{Age} x1.018 [if female] x 1.159 [if Black]

SCr = standardized serum creatinine (µmol/L)

κ = 61.9 (females) or 79.6 (males)
α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of SCr/κ or 1
max = indicates the maximum of SCr/κ or 1
age = years

10.4 EQUATIONS FOR D_{LCO} ADJUSTMENT FOR HAEMOGLOBIN

- For new patients, 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)

  Percent predicted D_{LCO} corrected for Hb = [actual DLCO/ D_{LCO} predicted corrected for Hb] x 100%

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

  Percent predicted D_{LCO} corrected for Hb = [actual DLCO/ D_{LCO} predicted corrected for Hb] x 100%

10.5 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 10.5: 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 10.5: 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 10.5: 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 10.5: 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 10.5: 5 Predicted equations for Blood Pressure: white girls aged 11- 17 years (from [P04-08733])

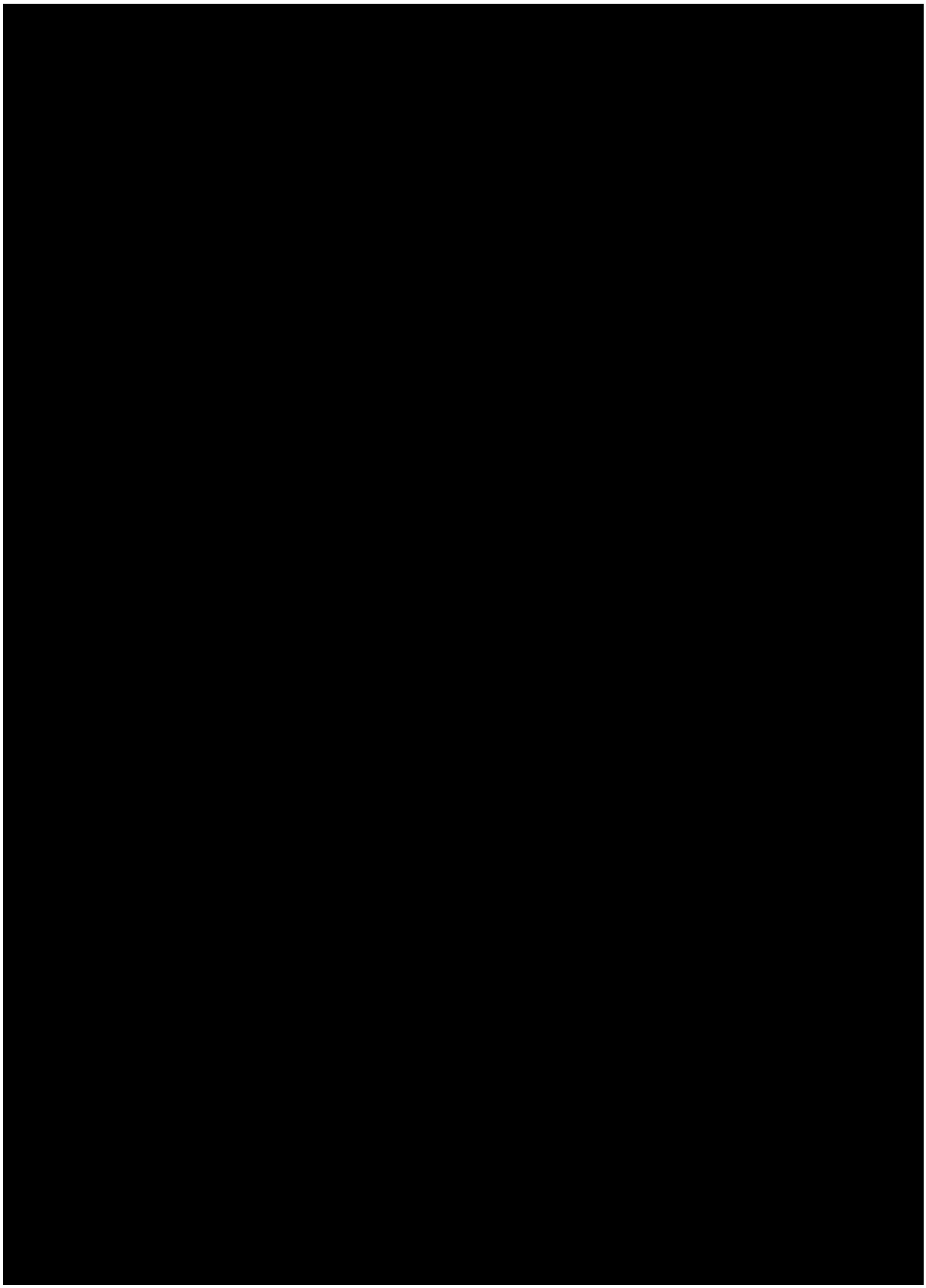
Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

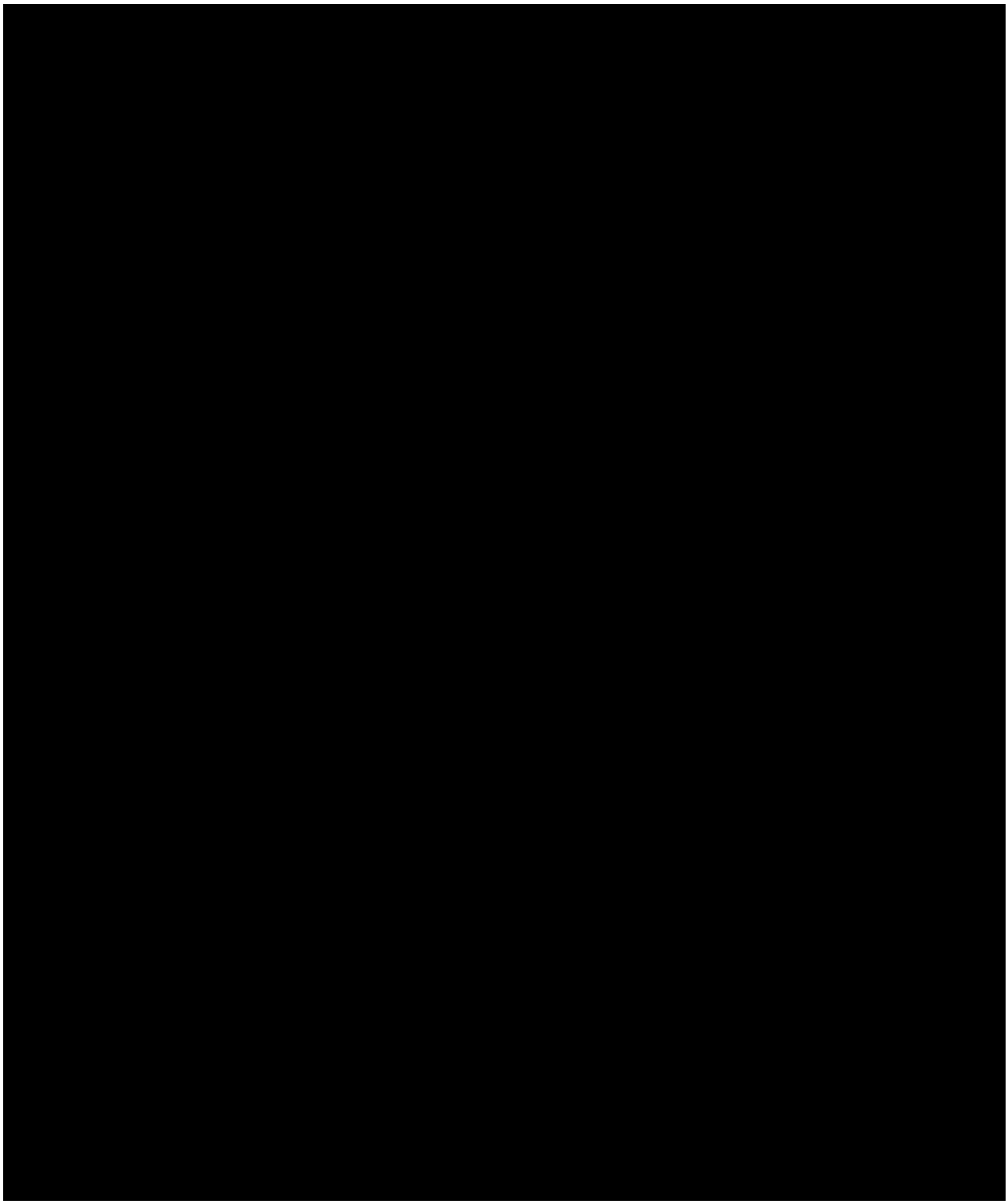
Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	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

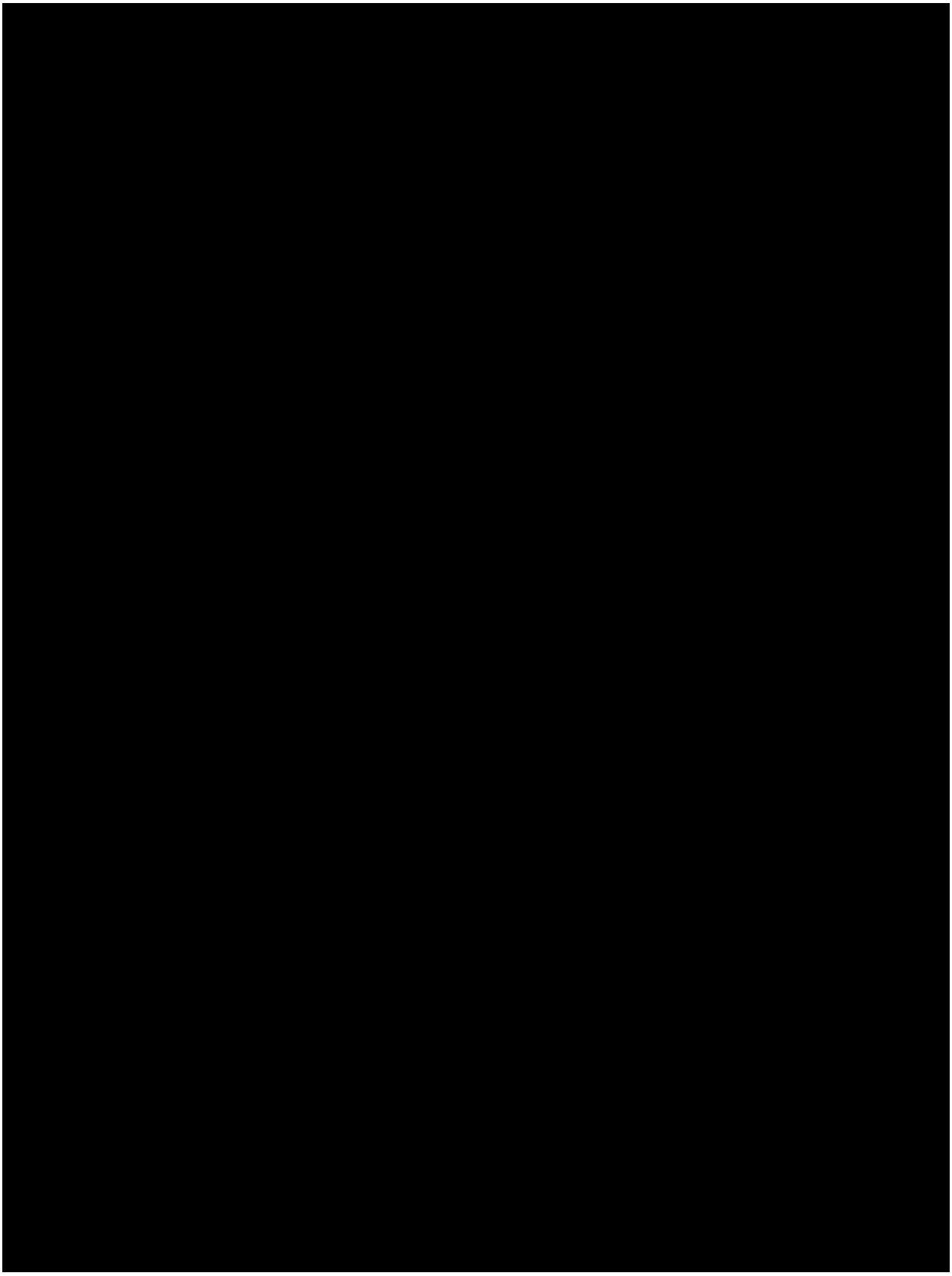
BP, blood pressure

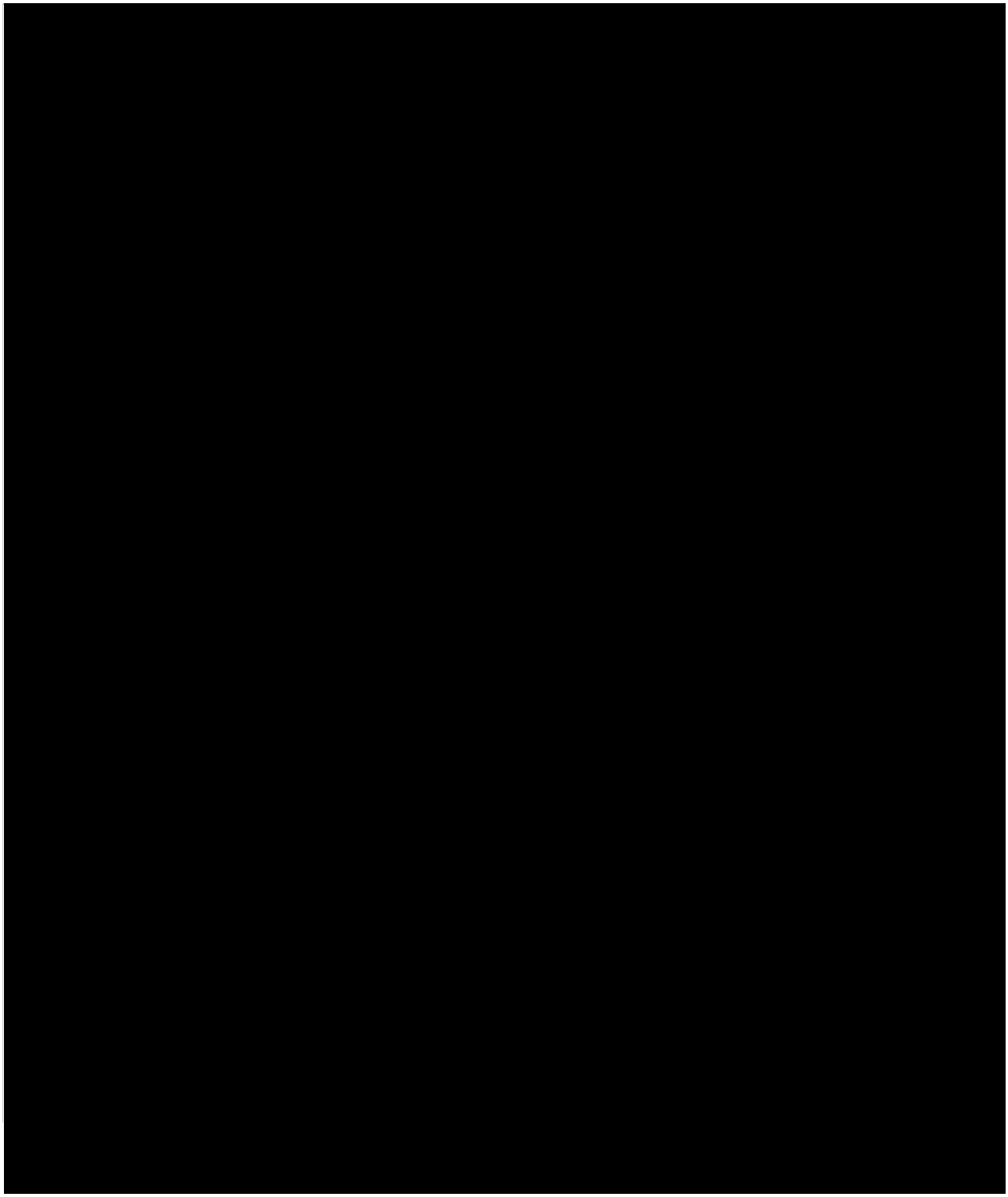
* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

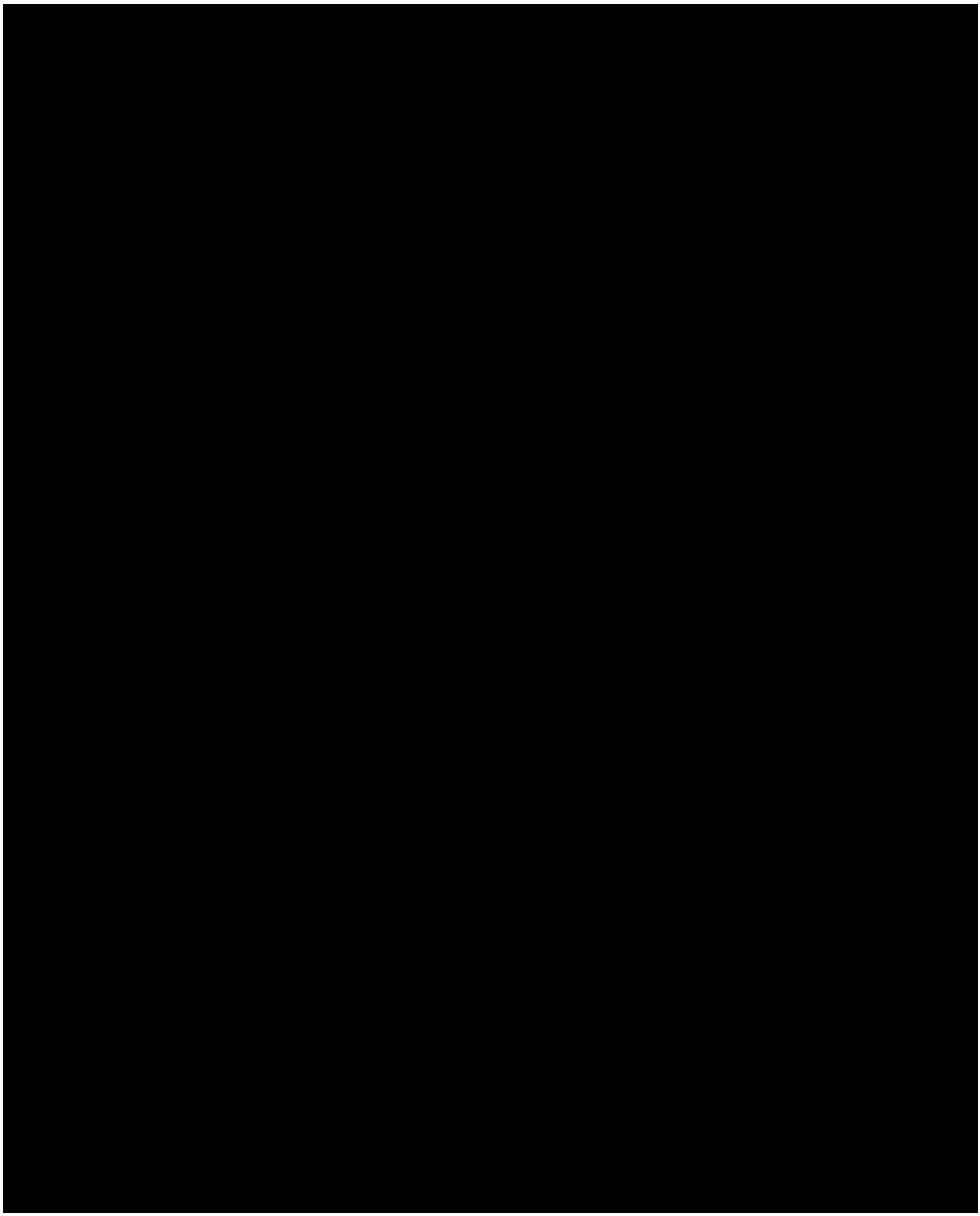
For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given 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.

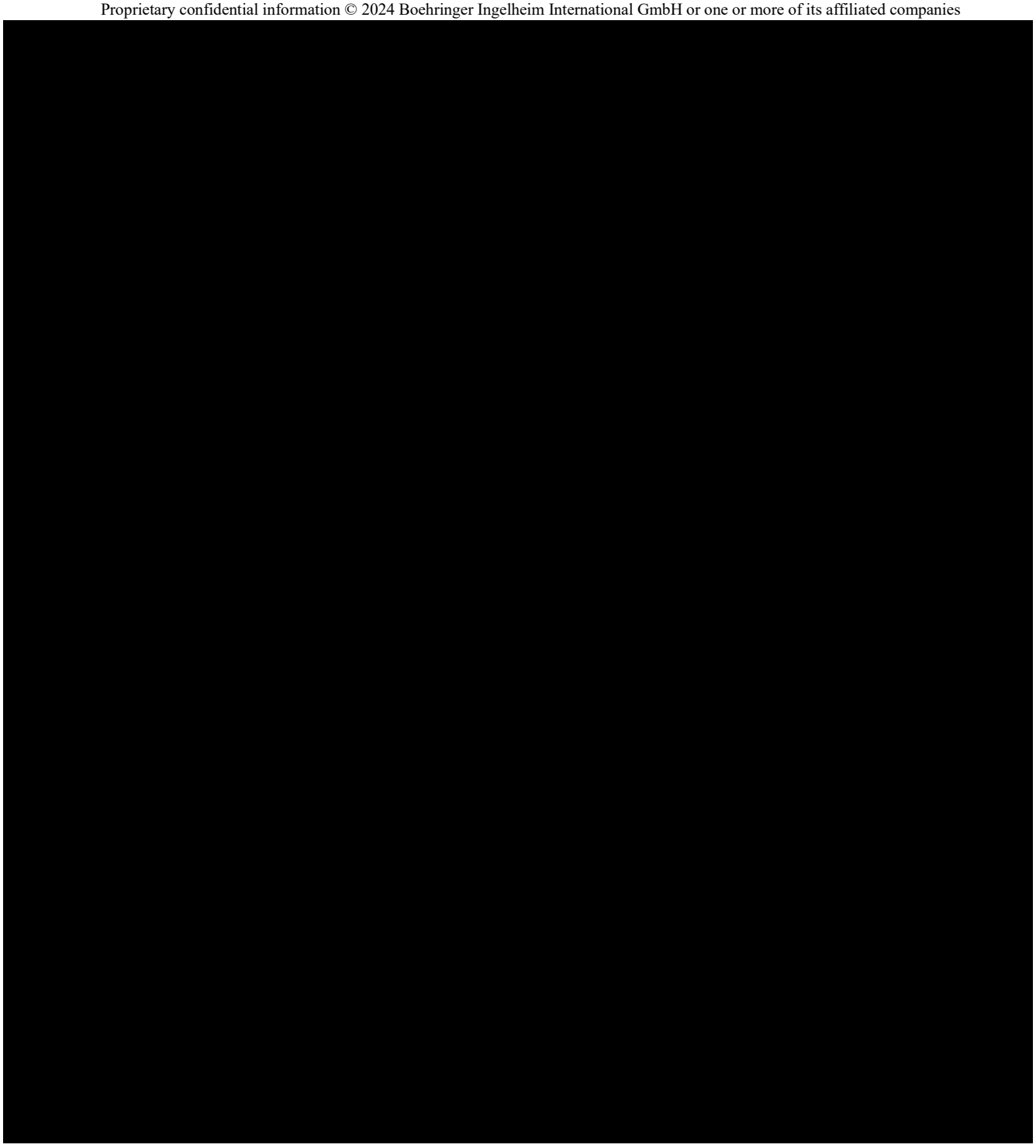


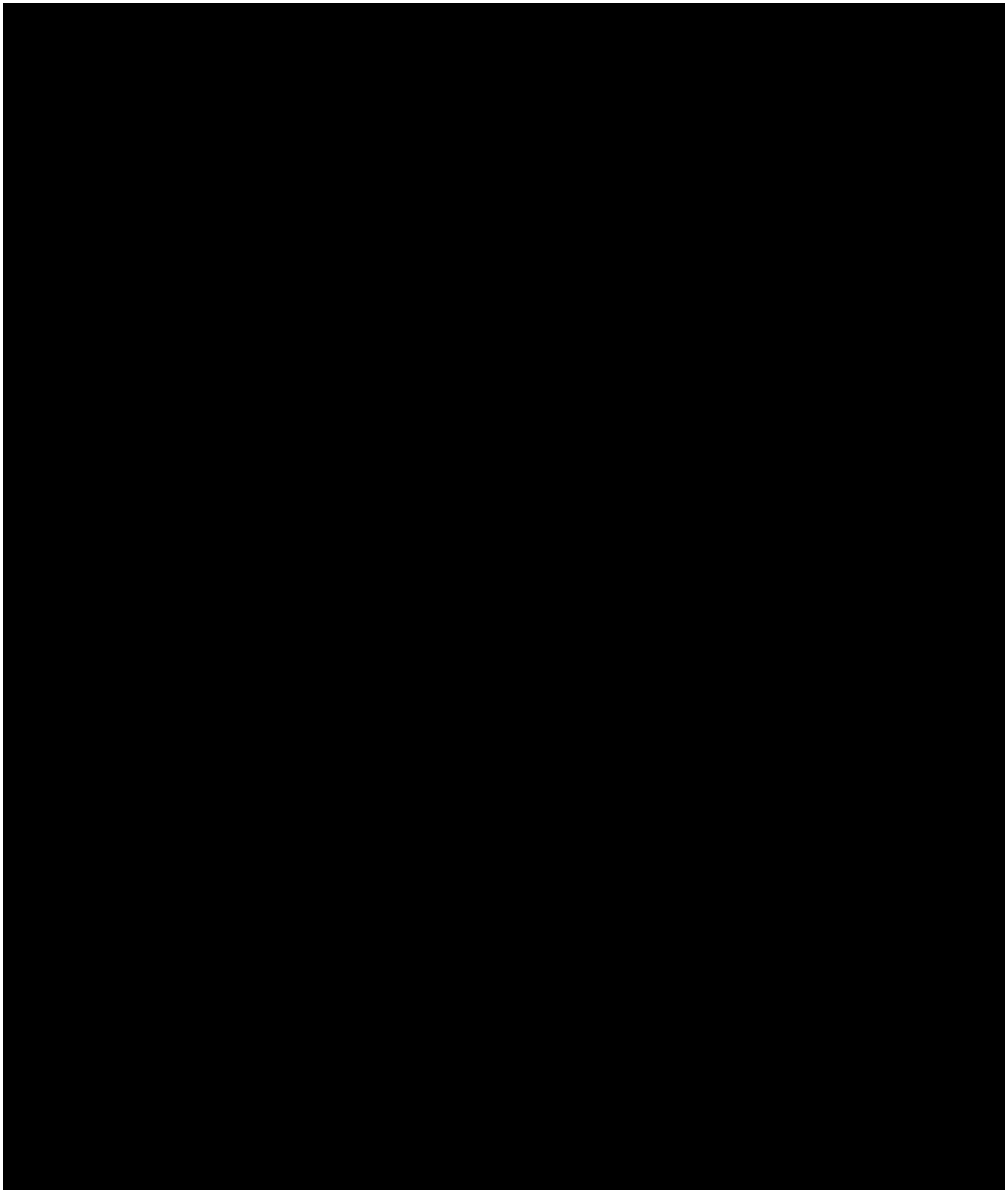


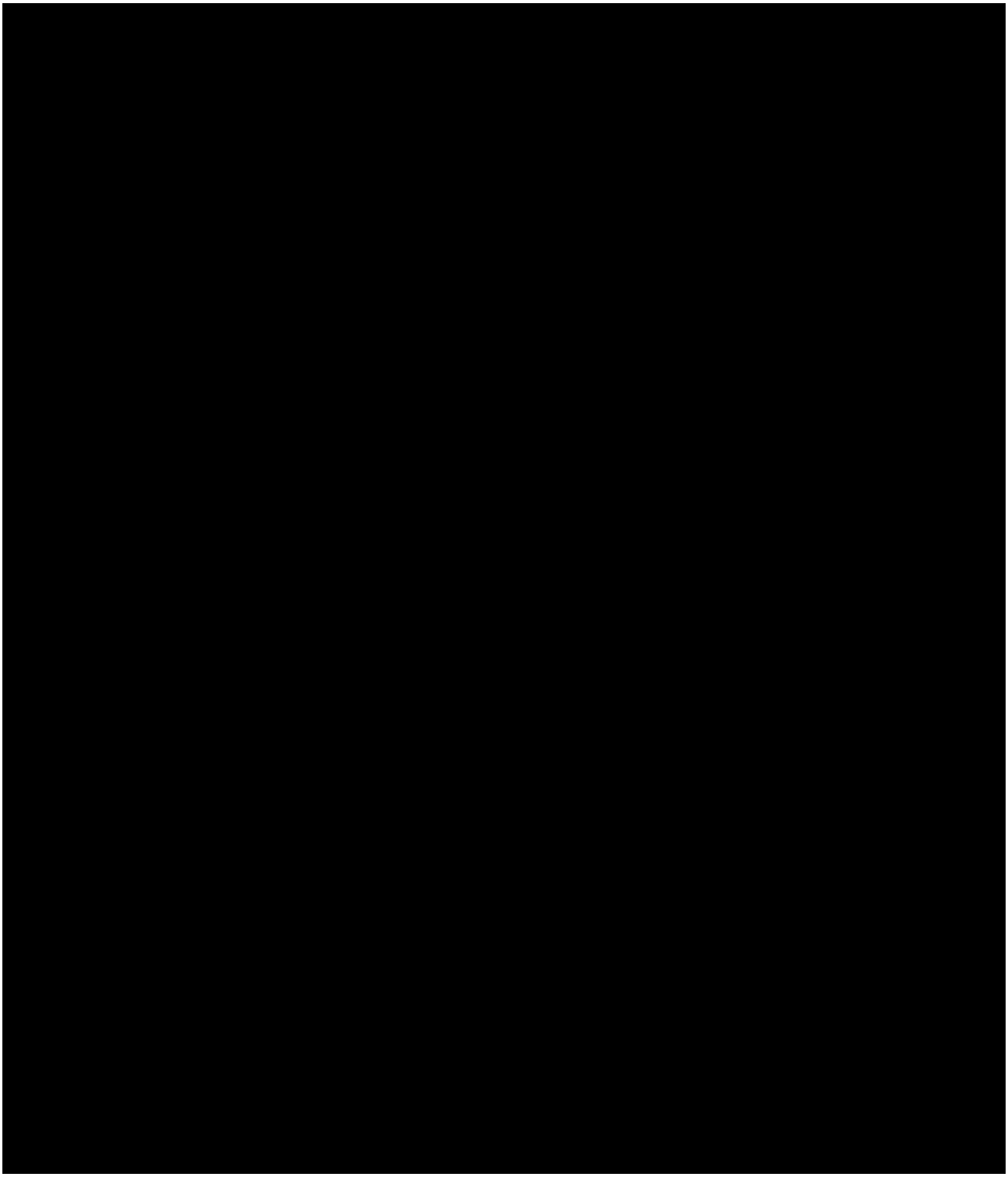


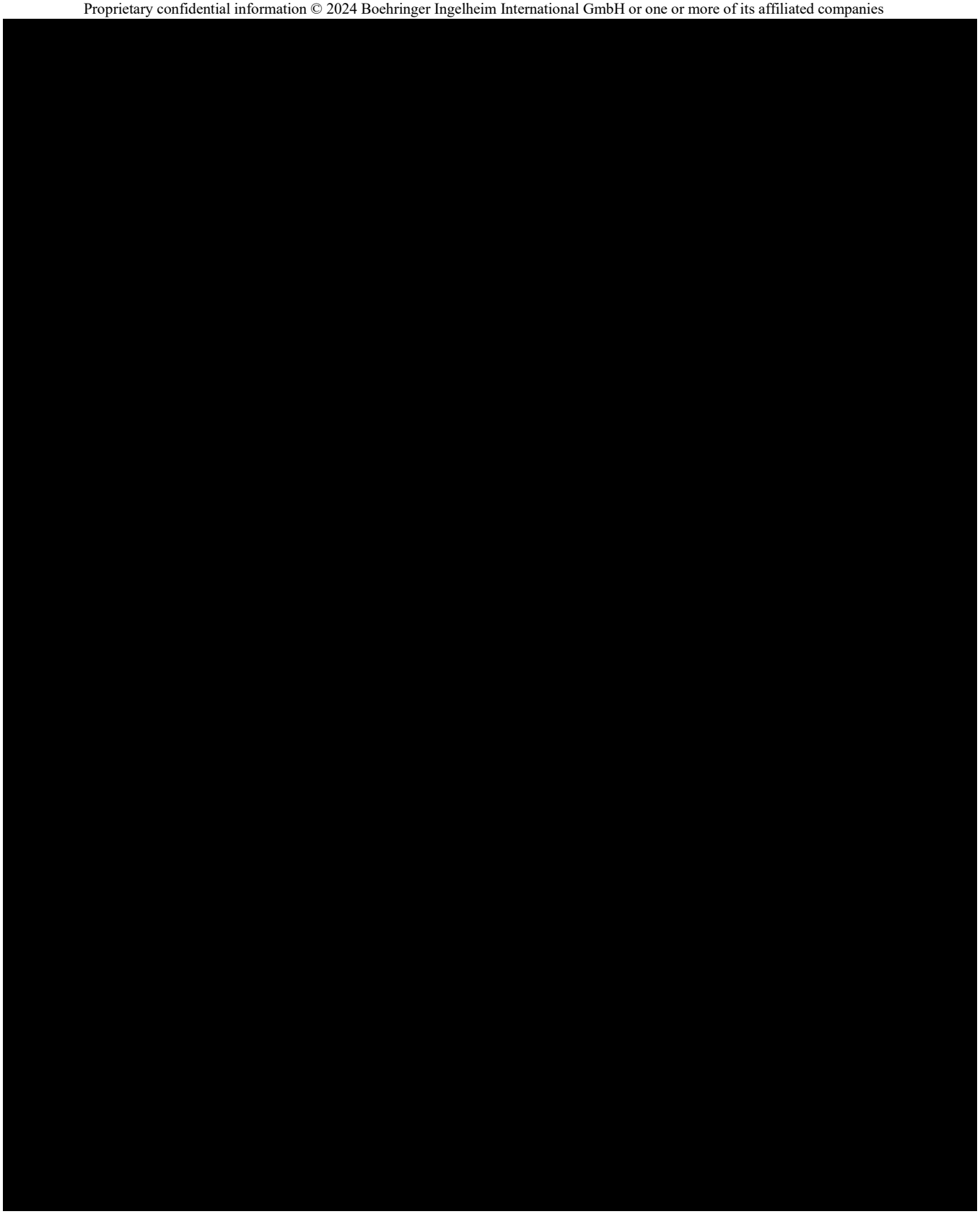


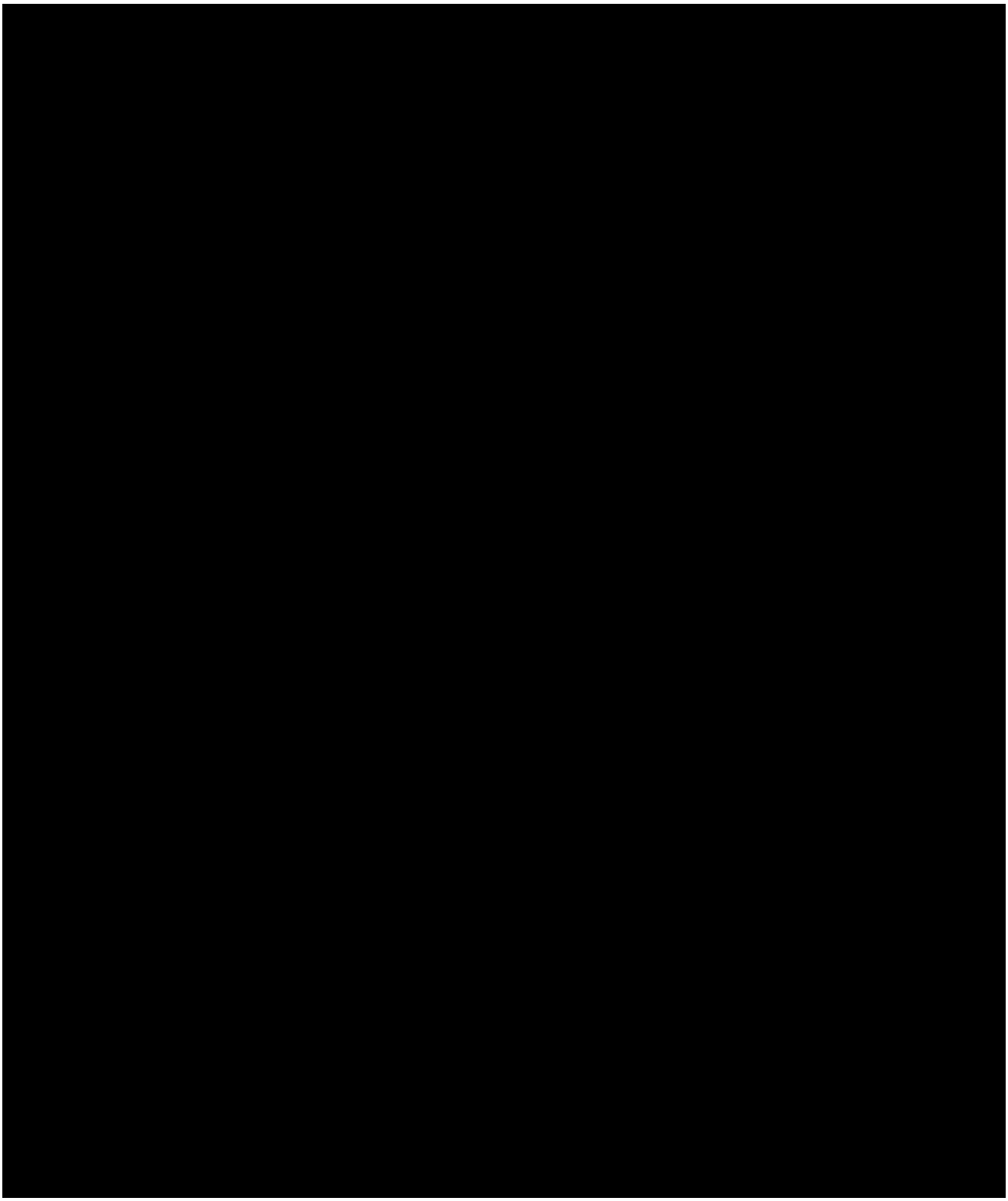


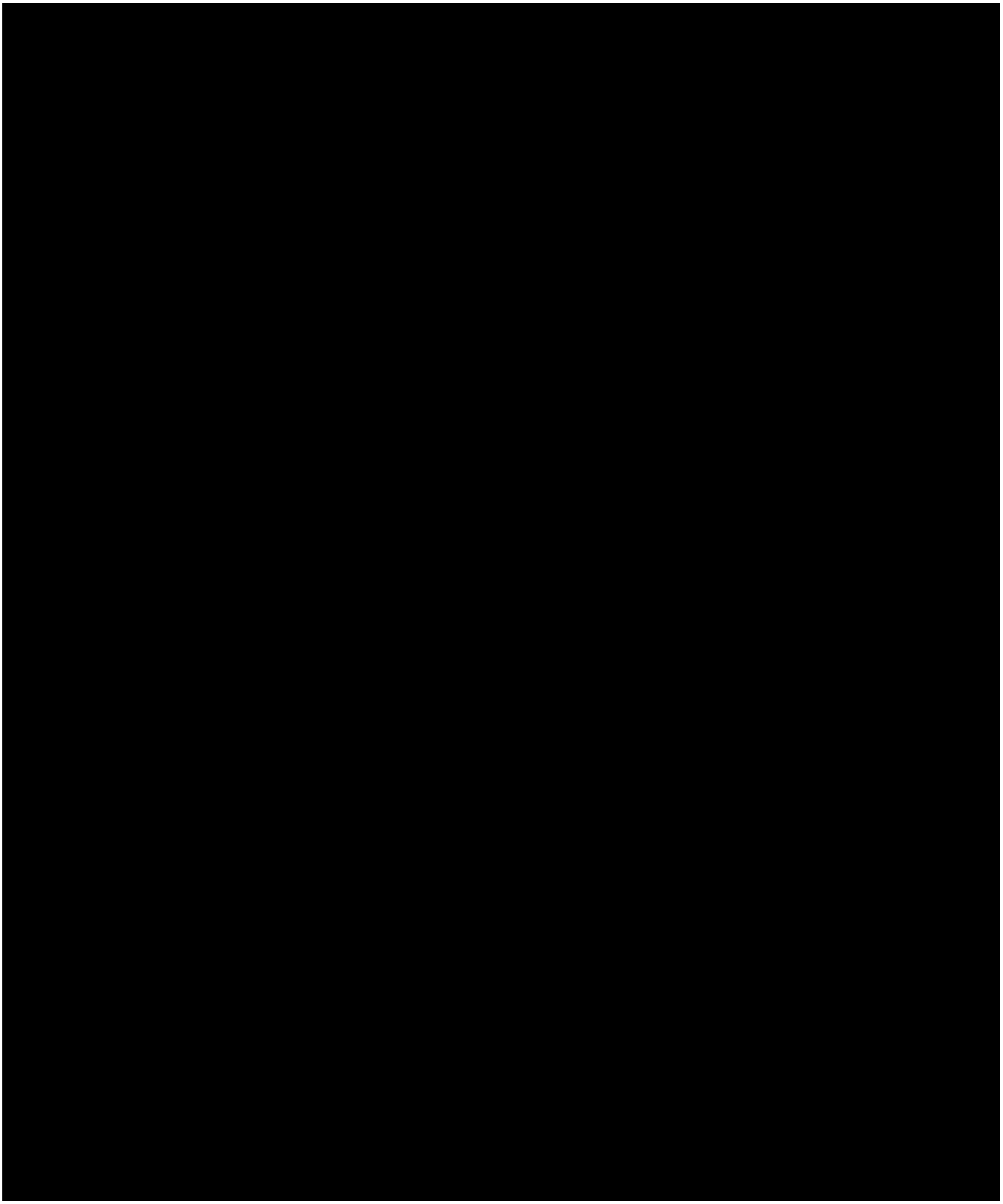


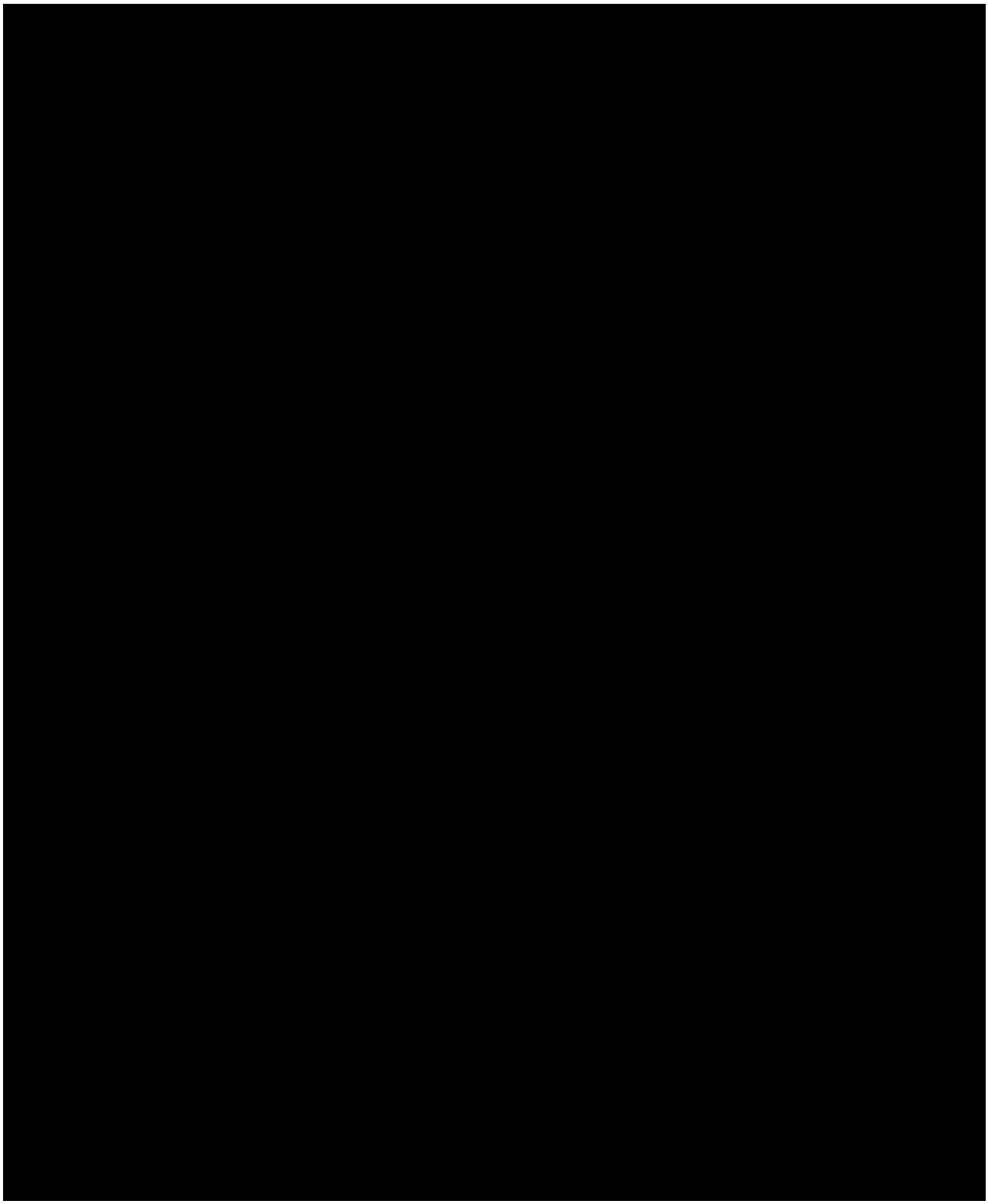


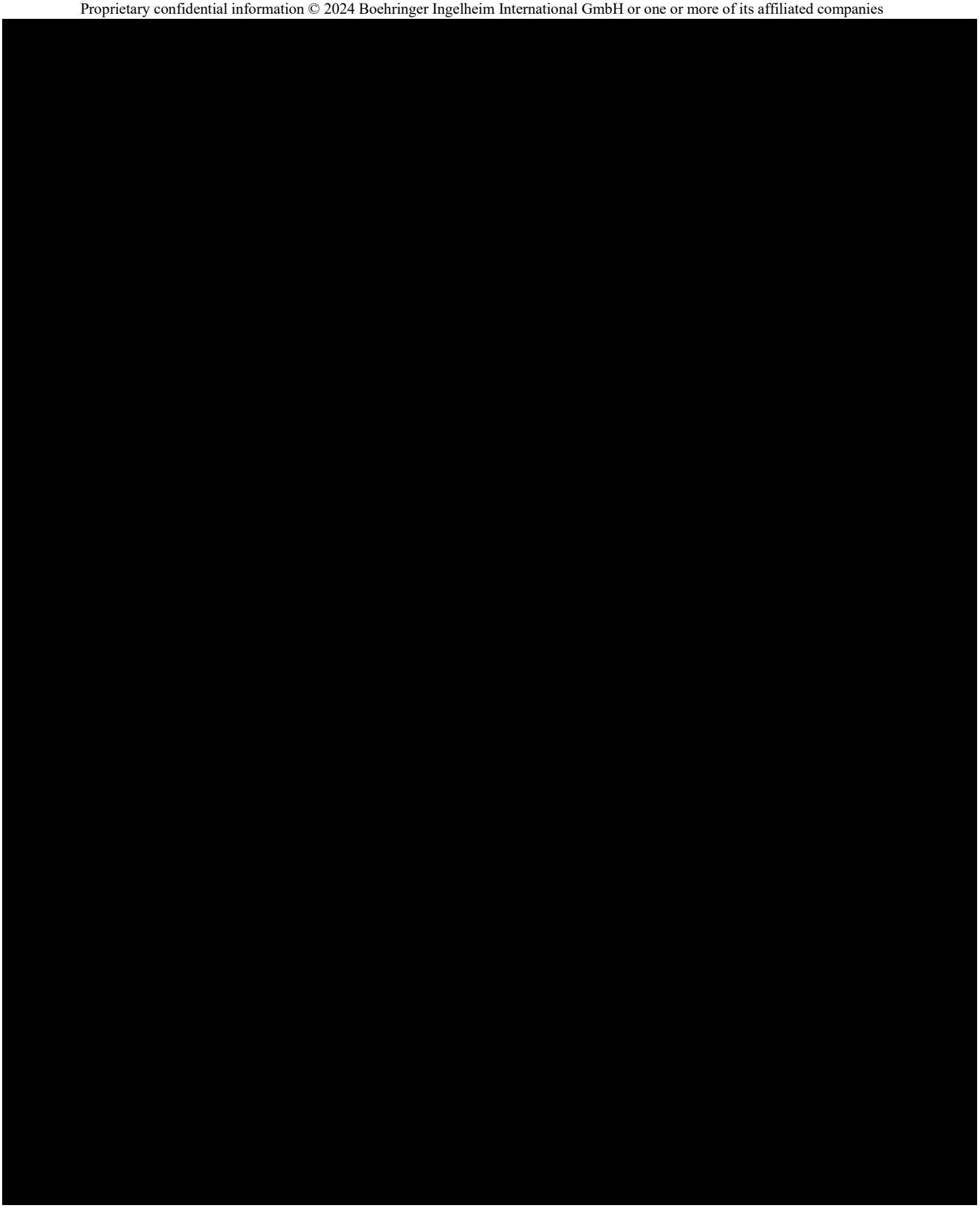


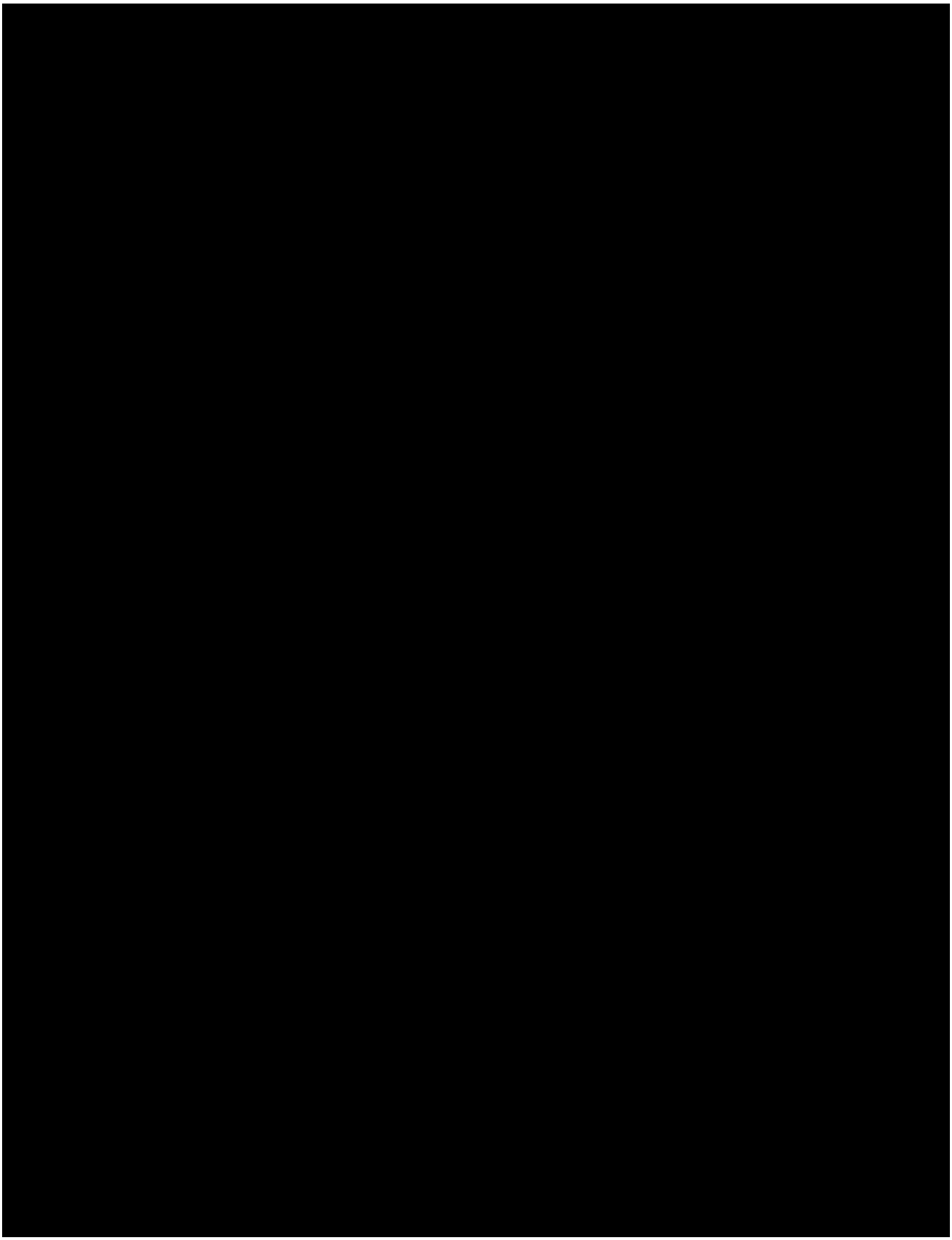


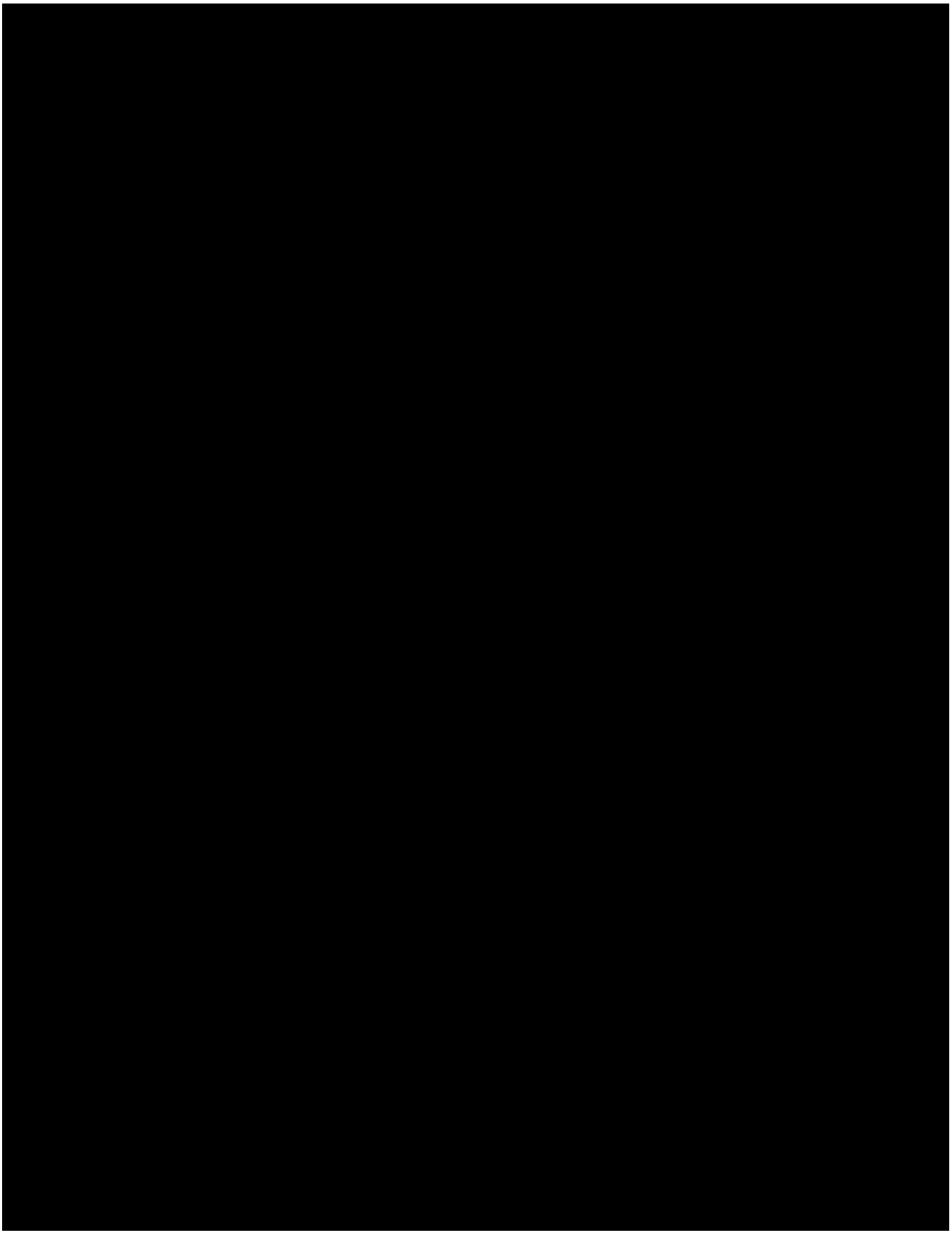


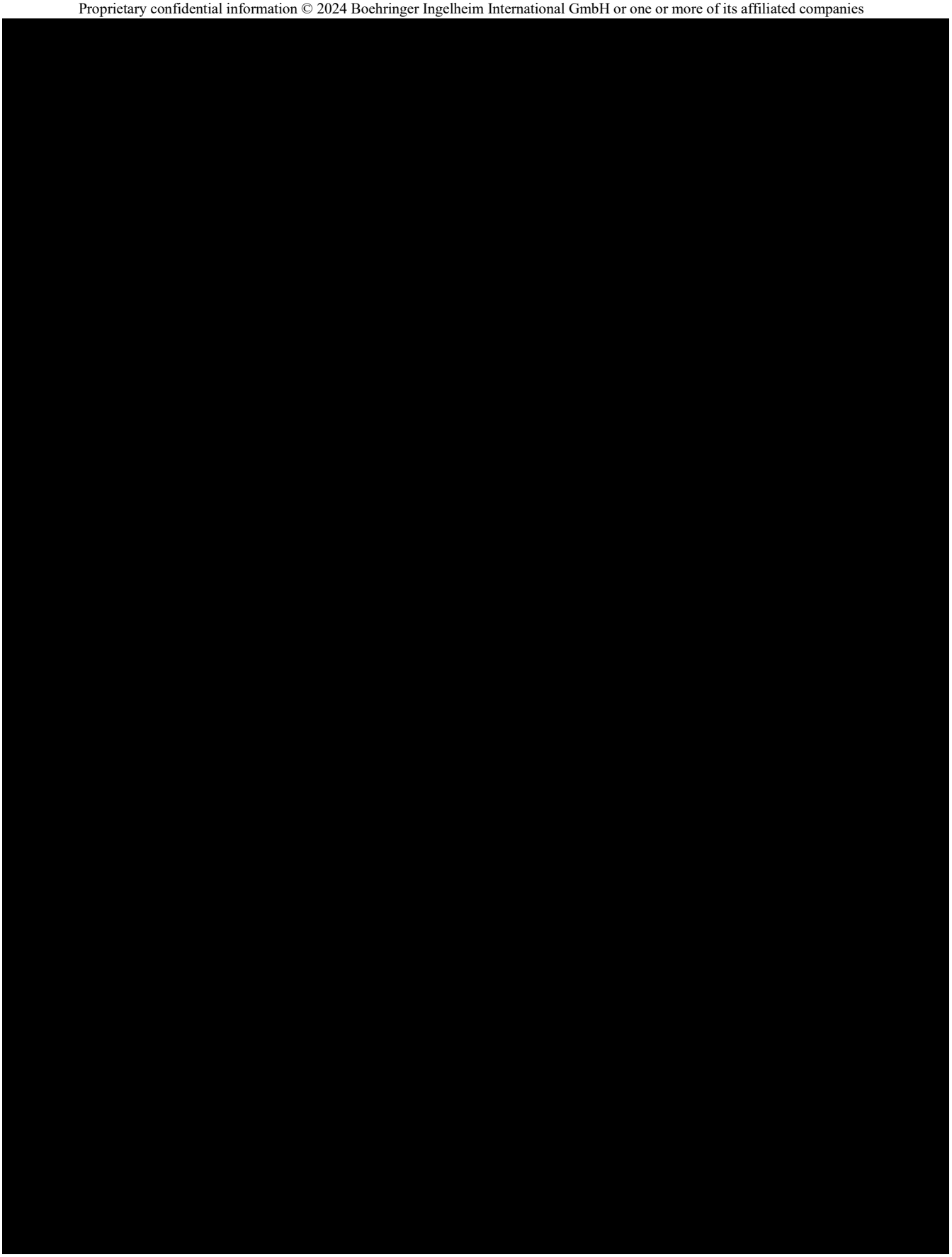


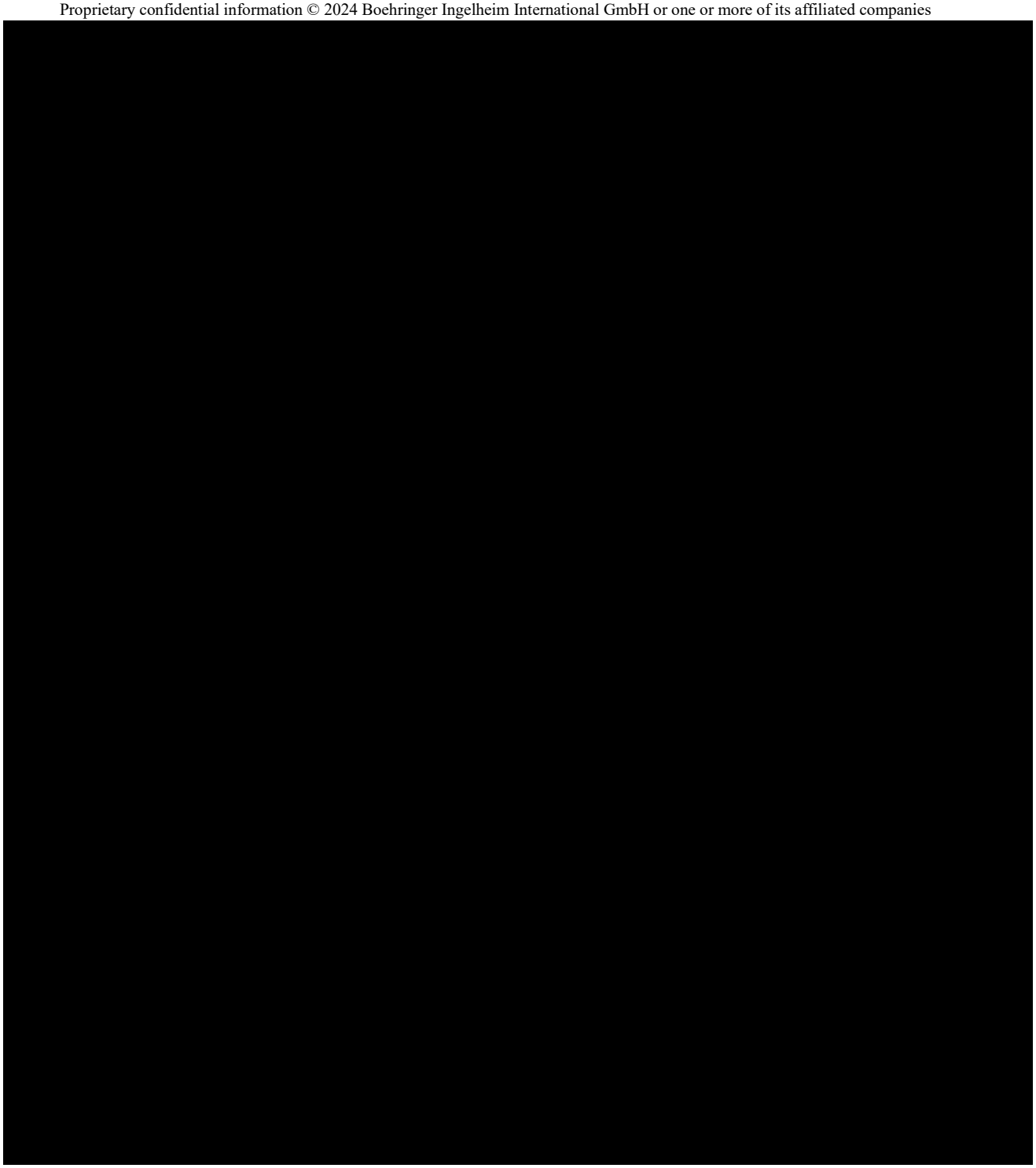












10.9 VISIT MODIFICATION IN EXCEPTIONAL CIRCUMSTANCES

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

INITIAL / STANDARD	MODIFIED or ADDED
Face-to-face patient visit performed by an adequate site staff under the responsibility of a physician on site.	• **for Visit 3 (when applicable) and Visit 4: 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 following visits, visits may be converted to home visits/combined home and remote visits. **if physical exam, vital signs, height, weight cannot be performed at least every 16 weeks, it needs to be considered that individual patient treatment needs to be interrupted upon discussion with sponsor.** Medical decision has to be documented in patient's source notes. **Home visit** performed (with portable stadiometer, tape, scale, ECG machine, [redacted] by the (sub)investigator or delegated to trained personnel to complete at least: • Physical examination and vital signs • Height sitting and standing • Leg length • Weight • ECG • [redacted] • 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 panoramic x-ray and bone MRI/x-ray to site (when needed) • Collect medication for IMP compliance • Assessments listed under "Investigator Call" if not done by separate call

INITIAL / STANDARD	MODIFIED or ADDED
	Investigator Call: The following assessments could be completed by (sub)investigator via phone or telemedicine, if not done during the home visit: [redacted] • AEs, SAEs, AESI • Trial medication and concomitant medications • Questionnaires administered as an interview using printed questionnaires • Pregnancy status and pregnancy diary completion check <u>The following assessments cannot be made outside investigational site</u>: • FVC, [redacted] FVC, [redacted] and [redacted] will be missed if the scheduled visit is converted to home visit, or combined home and remote visit. [redacted]
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 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

INITIAL / STANDARD	MODIFIED or ADDED
	• Testing must occur every 4 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. **If pregnancy tests cannot be conducted every 4 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 (except at the one time alignment with clinic visits).** Medical decision has to be documented in patient's source notes.
Dispensation of trial treatment 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/parent(s)/legal guardian must consent to provide contact details for shipping purposes • The patient/parent(s)/legal 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 AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		05 Aug 2022
EudraCT number **EU number**		2020-005554-23
BI Trial number		1199-0378
BI Investigational Medicinal Product(s)		Ofev®, nintedanib
Title of protocol		An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 2 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		All sections in the protocol (when applicable)
Description of change		InPedILD™ and InPedILD™-ON replaced by InPedILD® and InPedILD®-ON
Rationale for change		Administrative change
Section to be changed		Synopsis-Trial rationale and Section 1.3 Rationale for performing the trial
Description of change		Sentence below updated: The rationale of this open label trial is to collect additional safety and efficacy data of nintedanib in children and adolescents with clinically significant fibrosing ILD for at least 2 years **(applies to patients rolling-over from the parent trial)** or until alternative treatment options become **or are made available (e.g., via marketing authorization, via compassionate use or via similar process) (applies to new patients and to roll-over patients after 2 years).**
Rationale for change		To specify the trial rationale by patient's category
Section to be changed		Synopsis – main inclusion and exclusion criteria and Section 3.3.3 - Exclusion criteria 3
Description of change		Exclusion criteria 3 updated: (eGFR) <30 mL/min/**1.73m²** ~~calculated by Schwartz formula~~ at Visit 1(please refer to Appendix 10.3)
Rationale for change		Correction of eGFR unit and reference to Schwartz formula removed to be consistent with Appendix .

Section to be changed		Synopsis –Duration of treatment, Section 3.1 overall trial design, Figure 3.1:1 and Section 6.2.2 Treatment period(s) - treatment period duration
Description of change		Treatment duration for each patient will be variable. New patients will stay in the trial until the overall end of the trial (with expected minimum treatment duration of 24 weeks) or, if earlier, until alternative treatment options become or are made available (e.g. via marketing authorization, via compassionate use, or via similar process) to the patient outside of the clinical trial.
Rationale for change		Change of study treatment duration for new patients by removal of minimum treatment duration of 2 years.
Section to be changed		Synopsis –Duration of treatment and Section 3.1 overall trial design
Description of change		Sentence added to specify when the end of trial is expected: **The overall end of trial will take place approximately when last roll-over patient reaches 2 years of treatment ensuring that nintedanib or alternative treatment options (e.g. via marketing authorization, via compassionate use or via similar process) will be available for all remaining patients (roll-over or new patients) outside the trial at this time** [redacted]
Rationale for change		Clarification on the overall end of trial as it will be earlier than initially planned
Section to be changed		Flow Chart – time window F-up/EoS
Description of change		Time window added: +7 days
Rationale for change		To allow flexibility
Section to be changed		Flow Chart – criteria for dose reduction/interruption check + footnote 29
Description of change		"dose reduction/interruption check" added only for roll-over patients at V2, and removed at EOT for all patients
Rationale for change		reduction/interruption may be needed at V2 for roll-over patients and is not applicable at EOT for all patients
Section to be changed		Flow Chart – Vital status data + footnote 25
Description of change		Vital status added at EoS for new patients
Rationale for change		Vital status may be needed for new patients prematurely discontinued
Section to be changed		Flow Chart –footnote 1

Description of change		Footnote 1 updated for roll-over patients
Rationale for change		To allow the possibility of roll-over patients to roll-over later than initially planned in case site is not ready to be initiated at the period of switch and to allow flexibility
Section to be changed		Flow Chart –footnote 6
Description of change		Footnote 6 updated for new patients
Rationale for change		To clarify that one screening HRCT only should not be older than 12 months and to be consistent with other sections of CTP
Section to be changed		Flow Chart – footnote 21 Bone imaging
Description of change		Sentences below updated: For new patients: Imaging follow-up will be conducted at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks and every 24 weeks thereafter until the end of **study** or closure of the physes. For roll-over patients: **Not applicable for patients with closed physes at the end of InPedILD®.** Previous MRIs/x-rays within 12 weeks prior EoT/Visit 1/Visit 2 should be used as baseline **for roll-over patients with less than 52 weeks in InPedILD®. Previous MRIs or x-rays of epiphyseal growth plates within 24 weeks prior Visit 2 should be used as baseline for roll-over patients with more than 52 weeks in InPedILD®.** Imaging follow-up will be conducted, irrespective of scheduled visits, every 12 weeks in the following year after **the start of the trial medication** in the parent trial (when applicable) and every 24 weeks thereafter until the end of the study or closure of the physes.
Rationale for change		To be consistent with other sections of the CTP
Section to be changed		Flow Chart — footnote 21 Bone imaging and Section 5.2.5 Assessment of pathological findings of epiphyseal growth plate
Description of change		Time window for timepoints of follow-up bone imaging updated as follow: If it is not possible to conduct the follow-up at the predefined time points, the procedure can be done **within 2 weeks before or 4 weeks after this time point with always minimum 10 weeks (first year)/22 weeks (thereafter) and always maximum 16 weeks (first year)/28 weeks**

		(thereafter) from previous procedure. Within this timeframe, timepoints may be adapted on a case-by-case basis by sponsor if appropriate for patient's safety.
Rationale for change		Revision of time window to allow flexibility while assuring patient safety
Section to be changed		Flow Chart – footnote 22 clinical dental examination
Description of change		Sentence below updated as follow: Imaging follow-up will be conducted, irrespective of scheduled visits, every 12 weeks in the following year after **the start of the trial medication** in the parent trial (when applicable) and every 24 weeks thereafter until the end of the study or closure of the physes.
Rationale for change		To be consistent with other sections of the CTP
Section to be changed		Flow Chart – footnote 22 clinical dental examination and Section 5.2.6 Assessment of pathological findings on dental examination or imaging
Description of change		Time window for timepoints of follow-up dental examination updated as follow: If it is not possible to conduct the follow-up at the predefined time points, the procedure can be done **within 2 weeks before or 4 weeks after this time point with always maximum 16 weeks (first year)/28 weeks (thereafter) from previous procedure. Within this timeframe, timepoints may be adapted on a case-by-case basis by sponsor if appropriate for patient's safety.**
Rationale for change		Revision of time window to allow flexibility while assuring patient safety
Section to be changed		Flow Chart – footnote 23 Dental imaging
Description of change		Sentence below updated as follow: Imaging follow-up will be conducted, irrespective of scheduled visits, every 24 weeks in the following year after **the start of the trial medication** in the parent trial (when applicable) and every 48 weeks thereafter until the end of the study or closure of the physes.
Rationale for change		To be consistent with other sections of the CTP
Section to be changed		Flow Chart – footnote 23 Dental imaging and Section 5.2.6 Assessment of pathological findings on dental examination or imaging
Description of change		Time window for timepoints of follow-up dental imaging updated as follow:

		If it is not possible to conduct the follow-up at the predefined time points, the procedure can be done **within 2 weeks before or 4 weeks after this time point with always minimum 22 weeks (first year)/46 weeks (thereafter) and always maximum 28 weeks (first year)/52 weeks (thereafter) from previous procedure. Within this timeframe, timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety**.
Rationale for change		Revision of time window to allow flexibility while assuring patient safety
Sections to be changed		Flow Chart – footnote 24, Section 3.3.4 Discontinuation of patients from treatment or assessments and Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Description of change		In case of premature treatment discontinuation, new patients should attend remaining visits until the overall end of trial or, if earlier, until alternative treatment options become or are made available (e.g., via marketing authorization, via compassionate use or via similar process) to the patient outside the trial.
Rationale for change		Change of study treatment duration for new patients
Section to be changed		Flow Chart – footnote 26
Description of change		Footnote updated as below: End of Study (EoS), synonym **for individual patient's** end of trial.
Rationale for change		Clarification to differentiate patient's end of trial from "overall end of trial".
Section to be changed		Flow Chart – footnote 28 and Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Description of change		The last visit to be performed by new patients prematurely discontinued will be EoS including trial completion. This visit will be done at the overall end of trial or, if earlier, when treatment options become or are made available for new patients.
Rationale for change		Treatment duration of roll-over patients and new patients will be different
Section to be changed		Flow Chart – after footnote 29, Section 4.1.4 Drug assignment and administration of doses for each patient, Section 6.1 Visit schedule and Section

		8.3.2 Direct access to source data and documents
Description of change		War has been added as example of exceptional situation
Rationale for change		To ensure possible adaptations of protocol procedures in case of war in one country involved in the study.
Section to be changed		Flow Chart for [redacted]
Description of change		Table and footnote 2 updated to clarify that timepoints are calculated from start of medication in the parent trial: [redacted]
Rationale for change		Clarification
Section to be changed		Section 1.1 Medical background
Description of change		Sentence added: **As the underlying diseases associated with the clinically significant fibrosing Interstitial Lung Disease may be multiple, different regimes of immunosuppressives/ supportive symptomatic therapy are considered as standard of care for the treatment of ILD in children.**
Rationale for change		Definition of "standard treatment" added
Section to be changed		Section 1.1 Medical background
Description of change		Section updated with the current status of InPedILD® trial
Rationale for change		First results from InPedILD® DBL1 are now available
Section to be changed		Section 1.3 Rational for performing the trial
Description of change		Sentence below added: **Alternative therapies outside of the trial would be alternative drugs shown to have a positive benefit- risk assessment, any new therapy which would be available on the market for this indication or most probably the availability of nintedanib via marketing authorization, or via compassionate use or via similar process, as offered/provided by the sponsor (depending on local laws).**
Rationale for change		Definition of alternative treatments added
		Section 1.3 rationale for performing the trial
		Sentence below added: **It is expected that availability of nintedanib via marketing authorization, or via compassionate use or via similar process, as offered/provided**

		by the sponsor (depending on local laws) occurs approximately when last roll-over patient reaches 2 years of treatment [redacted]
		To clarify that availability of nintedanib outside the trial is expected at the time of the overall end of trial
Section to be changed		Section 1.4.2 Risk - Table 1.4.2:1 Overview of trial related risks
Description of change		Sentences below have been replaced for "Impact on bone development and growth": ~~Impact on Previous MRIs or x-rays of epiphyseal growth plates within respectively 12 weeks or 24 weeks prior baseline may be used at baseline for patients coming from InPedILD™ with respectively less or more than 52 weeks in InPedILD™.~~ **Please refer to Flow Chart footnotes and to CTP Section 5.2.5 for more details.**
Rationale for change		To be consistent with other sections of the clinical trial protocol related to Bone imaging
Section to be changed		Section 1.4.2 Risk - Table 1.4.2:1 Overview of trial related risks
Description of change		Sentences below have been replaced for "Impact on dentition": ~~Previous dental examination within 12 weeks prior baseline may be used at baseline.~~ **Please refer to Flow Chart footnotes and to CTP Section 5.2.6 for more details.** ~~Previous panoramic x-ray within 24 weeks prior baseline may be used at baseline.~~ **Please refer to Flow Chart footnotes and to CTP Section 5.2.6 for more details.**
Rationale for change		To be consistent with other sections of the clinical trial protocol related to Dental imaging and dental examination
Section to be changed		Section 1.4.2 Risk - Table 1.4.2:1 Overview of trial related risks
Description of change		Sentences below have been added for "radiation exposure": **MRI/x-ray required with minimum 10 weeks (first year)/22 weeks (thereafter) and maximum 16 weeks (first year)/28 weeks (thereafter) from the previous procedure, taking into account, for roll-over patients, the participation in the parent trial. Similarly,** MRI/x-ray at EoT

		required only if previous MRI/x-ray not available within 12 weeks in the first year, 24 weeks thereafter. **Within this timeframe, timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety**
Rationale for change		To be consistent with other sections of the clinical trial protocol related to Bone imaging and Dental imaging
Section to be changed		Section 1.4.3 Discussion
Description of change		Status of this trial has been updated
Rationale for change		To clarify that now this extension trial is started
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Section 3.1 Trial design
Description of change		Figure 3.1:1 of Trial design has been updated for group of new patients
Rationale for change		Recruitment period for new patients will be reduced and treatment duration for new patients will be variable
Section to be changed		Section 3.1 Trial design
Description of change		Complete section revised to include change of treatment duration between roll-over patients (at least 2 years) and new patients (variable duration

		of treatment)
Rationale for change		Change of study treatment duration for new patients and consequences of this change
Section to be changed		Section 3.1 Trial design
Description of change		Introduction of new category of patients: completed patients not able to roll over into the extension trial within 12 weeks following their End of Treatment in the parent trial (i.e. time period between last dose of study drug in parent trial and first dose in extension trial is greater than 12 weeks). These patients will be handled as new patients in 1199-0378, i.e. they have to follow the visit schedule for new patients but will have adapted inclusion/exclusion criteria.
Rationale for change		New group of patients has been identified for the trial and for the trial analysis
Section to be changed		Section 3.1 Trial design
Description of change		Description of the overall end of trial has been updated
Rationale for change		To clarify when will be EoT visit for remaining patients at the overall end of trial
Section to be changed		Section 3.1 Trial design and Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Description of change		Sentences below adapted/added: If patients are not able to complete the remaining scheduled visits, a follow-up (FU) visit should be planned for 28 days after EoT. In addition, every attempt will be made to get information on vital status, when applicable, at 24 weeks, 52 weeks, 76 weeks and 104 weeks **and for new patients at EoS.** (…) **For new patients who prematurely discontinued trial drug, if nintedanib or alternative treatment options become or are made available outside the clinical trial before the overall end of trial, then vital status will be collected for the last time at that time and this will define the end of patient's participation in the trial (trial completion).**
Rationale for change		Update related to collection of vital status for new patients as change in study treatment duration for new patients
Section to be changed		Section 3.3 Selection of trial population

Description of change		Reduction of recruitment period from 2 year to 18 moths, increase of number of sites from 30 to around 40, and reduction of number of countries from 23 to 21.
Rationale for change		Reduction of trial duration and to reflect actual number of sites/countries.
Section to be changed		Section 3.3 Selection of trial population
Description of change		Sentence below updated as follow: Re-enrolment of screen failed patients will be permitted once. Patients who did not qualify for **entering treatment** during the early months of the recruitment period might qualify for **entering treatment** during the late months of the recruitment period of the study.
Rationale for change		Correction of wording as there is no randomisation but only treatment entry in this trial
Section to be changed		Section 3.3.2 Inclusion criteria and Section 3.3.3 Exclusion criteria
Description of change		Sentence below updated as follow: For patients who **prematurely** discontinued treatment permanently in 1199-0337 but are potentially eligible
Rationale for change		Clarification
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		Sentences below updated as follow: For patients who prematurely discontinued treatment permanently in 1199-0337 but are potentially eligible **and for completed patients from the parent trial, not able to roll over into the extension trial within 12 weeks following their End of Treatment Visit in the parent trial:** **Inclusion** criteria for new patients are applicable except criteria 4, and 6 (as eligibility for these criteria has been **confirmed already** in 1199-0337 and does not need to be repeated) **and also except inclusion criterion 1 for completed patients from the parent trial not able to roll over within 12 weeks following their End of Treatment Visit in the parent trial.**
Rationale for change		To mention inclusion criteria of new category of patients: completed patients not able to roll over within 12 weeks following their EoT in the parent trial.
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		Sentences below updated as follow: For patients who **prematurely** discontinued

		treatment permanently in 1199-0337 but are potentially eligible **and for completed patients from parent trial not able to roll-over into the extension trial within 12 weeks following their End of Treatment Visit in the parent trial**: All exclusion criteria for new patients are applicable**. In addition, the** following additional exclusion criterion **is applicable for patients who prematurely discontinued treatment permanently in 1199-0337**: 21. Patients who experienced drug-related adverse events during parent trial leading to permanent study treatment discontinuation.
Rationale for change		To mention exclusion criteria of new category of patients: completed patients not able to roll over within 12 weeks following their EoT in the parent trial.
Section to be changed		Section 3.3.4.1 Discontinuation of trial treatment
Description of change		Sentence below added: **In case, the laboratory results at Visit 2 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. In the patient's medical records.**
Rationale for change		Clarification added to be consistent with note mentioned in CTP section 3.3.3 related to exclusion criteria 3
Section to be changed		Section 3.3.4.3 Discontinuation of trial by sponsor
Description of change		One reason for trial discontinuation added: **Alternative drugs shown to have a positive benefit- risk assessment/ any new therapy available on the market for this indication or the availability of nintedanib via marketing authorization, or via compassionate use or via similar process, as offered/provided by the sponsor (depending on local laws)**.
Rationale for change		Clarification that trial may be discontinued by sponsor when any new therapy available on the market for this indication or when availability of nintedanib outside the trial
Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		Following sentence removed: ~~Once smaller capsules have been assigned, IRT will not allow to switch back to bigger capsules~~

Rationale for change		To give possibility for patient to switch back to larger capsules if appropriate
Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		One sentence adapted: **If needed, an** unscheduled visit can be registered in IRT at any time during the course of the trial **to register a dose change, to obtain additional kit(s) or to** obtain kits with smaller or **larger** capsules.
Rationale for change		To clarify when unscheduled visit is needed
Section to be changed		Section 4.2.1.2 Management of liver enzyme elevation -Table 4.2.1.2:1 Clinical evaluation of hepatic injury
Description of change		one recommendation updated and new footnote added in the table (footnote 5).
Rationale for change		Recommendations for managing liver enzyme elevation updated
Section to be changed		Section 4.2.1.2 Management of liver enzyme elevation -Table 4.2.1.2:1 Clinical evaluation of hepatic injury
Description of change		Footnote 4 updated
Rationale for change		Clarification
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Duration of bronchodilators updated to: Withhold short–acting bronchodilators for **at least** ~~more than~~ 8 hours before the assessments, - Withhold long–acting bronchodilators for **at least** ~~more than~~ 24 hours before the assessments.
Rationale for change		Clarification to be consistent with other sections of CTP
Section to be changed		Section 4.2.2.3 Contraception requirements
Description of change		Sentence updated: WOCBP (trial participant ~~or partner of a trial participant~~) 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 if their sexual partner is a man able to father a child.
Rationale for change		Correction to clarify that female partners of male patients receiving nintedanib are not required to follow contraceptive guidelines as mentioned already in the Investigator Brochure
Section to be changed		[redacted]
Description of change		Sentence below removed:

		~~This assessment will not be performed for new patients~~
Rationale for change		Clarification to be consistent with Flow Chart and other CTP section
Section to be changed		Section 5.2.1.2 Height, leg length
Description of change		Sentences below added: **For roll-over patients, the procedure followed to make these measurements for a given patient must be consistent with procedure followed in the parent trial as communicated to the site by the sponsor.**
Rationale for change		To assure consistency of measurements between parent trial and extension trial
Section to be changed		Section 5.2.3 Safety laboratory parameters - pregnancy test
Description of change		Sentence below updated: A pregnancy test diary card will be dispensed ~~(~~at ~~all~~visits **defined in the Flow Chart**~~for roll-over female patients, from Visit 3 for new female patients)~~
Rationale for change		Correction to be consistent with Flow Chart and other sections of protocol
Section to be changed		Section 5.2.3 Safety laboratory parameters – Table 5.2.3:1
Description of change		Table revised to remove parameter mentioned twice
Rationale for change		Correction
Section to be changed		Section 5.2.3 Safety laboratory parameters – Table 5.2.3:1 and Table 5.2.3:3
Description of change		Tables revised to specify that eGFR will be done only at V1 and V2
Rationale for change		eGFR to be done only at V1 and V2
Section to be changed		Section 5.2.5 Assessment of pathological findings of epiphyseal growth plate
Description of change		Senence below added: **For roll-over patients, the procedure followed to make these measurements for a given patient must be consistent with procedure followed in the parent trial.**
Rationale for change		Clarification
Section to be changed		Section 5.2.5 Assessment of pathological findings of epiphyseal growth plate
Description of change		Sentence below added: **Results of central review will be reported to the investigator. In case of pathological findings/potentially pathological findings on**

		Epiphyseal Growth Plate Results Report identified by central reviewer, the investigator should assess if these findings should be reported (AE/AESI) or not (see Section 5.2.7.1.4.).
Rationale for change		Clarification on assessment of imaging findings by investigator
Section to be changed		Section 5.2.6 Assessment of pathological on dental examination or imaging
Description of change		Sentence below added: **Results of central review will be reported to the investigator. In case of pathological findings /potentially pathological findings identified by central reviewer, the investigator should consult immediately the local dentist, to confirm, if these findings should be reported (AE/AESI) or not (see Section 5.2.7.1.4.).**
Rationale for change		Clarification on assessment of imaging findings by investigator
Section to be changed		Section 5.2.7.2.4 Safety monitoring and Adverse event with additional information collection and Section 8.7 administrative structure of trial
Description of change		Sentences below added: **Additionally, images of a particular patient may be reviewed by other radiology or clinical experts selected by sponsor for consultancy, if judged needed by the sponsor, to assess safety of this particular patient or to support overall safety assessment**
Rationale for change		To allow any additional external expert's review of bone imaging if judged needed for patient's safety.
Section to be changed		Section 5.2.7.2.4 Safety monitoring and Adverse event with additional information collection and Section 8.7 Administrative structure of trial
Description of change		Sentences below added: **Additionally, images of a particular patient may be reviewed by other external dentists/experts in pediatric dentistry selected by sponsor for consultancy, if judged needed by the sponsor, to assess safety of this particular patient or to support overall safety assessment**
Rationale for change		To allow any additional external expert's review of dental imaging if judged needed for patient's safety or to support overall safety assessment.
Section to be changed		Section 5.2.7.2.4 Safety monitoring and Adverse event with additional information collection and

		Section 8.7 Administrative structure of trial
Description of change		Sentence below added: **In parallel, the Adjudication Committee/a member of the Adjudication committee will review all dental findings of stunted growth of the dental root identified by central review to assess them to either pathological finding /stunted growth or not. Certain further dental findings may potentially be assessed if defined in the Adjudication Charter (dental imaging from 1199-0337 study may be included in this assessment process).**
Rationale for change		To add new assessment process for dental findings
Section to be changed		Section 6.2.2 Treatment period(s) – Visit 1/Visit2 for roll-over patients
Description of change		Section revised by updating following sentences: Blood and urine samples **for** ~~(~~safety laboratory tests, and [redacted] **(and** pregnancy test on serum in female patients only) (…) An additional blood sample to check **safety parameter(s)** [redacted] or the 1199-0378 study **may**~~will~~ be collected at the same time as blood and urine samples for EoT of 1199-0337. (…) [redacted]
Rationale for change		To reflect the different situations that could happened for blood samples collection
Section to be changed		Section 6.2.2 Treatment period(s) – Visit 1/Visit2 for roll-over patients
Description of change		Sentence below adapted: If a previous MRI **or x-ray** as outlined above, is not available, **imaging** ~~an MRI~~ of epiphyseal growth plates should be conducted according to protocol requirements
Rationale for change		To be consistent with other sections of protocol
Section to be changed		Section 6.2.2 Treatment period(s) – Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, X (treatment period)
Description of change		Sentence below updated: Additional clinic visits will be scheduled after 12, 24, 36, 52, 64, 76, 88 and 104 weeks of treatment (Visits 4 to 11) **and, when applicable, every 12**

		weeks (Visit X) thereafter.
Rationale for change		To be consistent with Flow chart
Section to be changed		Section 6.2.2 Treatment period(s) – Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, X (treatment period)
Description of change		Sentence below updated: Procedures to be conducted at predefined time points, irrespective of scheduled visits, **according to time window defined in the Flow Chart**~~.or if not, to be done in the week immediately before or after the pre-defined time point.~~ **If it is not possible to conduct the follow-up at the predefined time points, please refer also to footnotes 21, 22, and 23 in the Flow Chart.**
Rationale for change		Updated time windows for specific safety procedures (bone imaging, dental imaging, dental examination)
Section to be changed		Section 6.2.2 Treatment period(s) – End of Treatment
Description of change		One sentence added and one sentence adapted and corrected as below: Patients who discontinue trial treatment prematurely should undergo the EoT visit as soon as possible. **If a patient discontinues the study during a scheduled treatment visit, then the visit will be considered as an EoT visit. As consequence, roll-over** patients that discontinue trial treatment at week 104 should perform EoT visit instead of **Visit 11**~~visit 12~~.
Rationale for change		Clarification (and correction of typo to be consistent with Flow Chart)
Section to be changed		Section 6.2.3 Follow-up period and trial completion
Description of change		Following sentence updated/added: At week 104, for **roll-over** patients who prematurely discontinued trial treatment before Visit 11 and were able to stay in the trial until week 104. Sentence added: **At the end of the EoS Visit for new patients who prematurely discontinued trial treatment and were able to stay in the trial until the overall end of trial or, if earlier, until alternative treatment options become or are made available.** At F-up visit, for **roll-over** patients who

		prematurely discontinued trial treatment before Visit 11 and were not able to stay in the trial until week 104 or ~~for patients~~ who prematurely discontinued trial treatment after week 104 **and for new patients who prematurely discontinued trial treatment and were not able to stay in the trial until the overall end of trial or, if earlier, until alternative treatment options become available.**
Rationale for change		Clarification related to trial completion
Section to be changed		Section 7.2.1 General considerations
Description of change		Patients' groups for analysis updated: Patients will be analysed depending if and when they rolled over from the parent trial (Group 1: New Patients **[including patients who prematurely discontinued treatment permanently in 1199-0337, and completed patients from the parent trial not able to roll over into the extension trial within 12 weeks following their End of Treatment visit in the parent trial]** and patients from 1199-0337 placebo arm Part A –, Group 2: patients from 1199-0337 Part B and from 1199-0337 nintedanib arm Part A) and overall.
Rationale for change		To include all types of patients in the analysis
Section to be changed		Section 7.2.6 Safety analyses
Description of change		Sentence below updated: ~~Treatment~~**Patient** 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.
Rationale for change		Correction as treatment is the same in all groups
Section to be changed		Section 7.2.8 Interim analyses
Description of change		Sentences updated as follow: **One** ~~I~~interim ~~analyseis are~~**is** planned after 1 ~~and 2~~ **years**~~,~~ i.e. after all roll-over patients **completed the 52 weeks visit** ~~and the 104 weeks visit respectively~~ **or** prematurely discontinued from the trial. **Additional interim analyses could be performed upon request from Health Authorities or for publication purposes.** All the previous**ly** mentioned analys~~i~~es may be presented at each interim analysis. Further details will be provided in the TSAP.

Rationale for change		Removal of second interim analysis due to reduction of trial duration.
Section to be changed		Section 8.3.1 Source documents
Description of change		The list of relevant committee/vendor to which copies of source documents may be provided has been updated with: **and to any other radiology/clinical experts or to any other external dentist/experts in pediatric dentistry selected by the sponsor for consultancy**.
Rationale for change		To allow any additional external expert's review if needed
Section to be changed		Section 10.4 Equation for Dlco adjustement for heamoglobin
Description of change		The following formulas have been revised as below: In adolescents (and adult males) D_{LCO} predicted corrected for Hb = D_{LCO} predicted x (1.7Hb)/(10.22+Hb) **Percent predicted D_{LCO} corrected for Hb = [actual DLCO/ D_{LCO} predicted corrected for Hb] x 100%** In children <15 years of age and females D_{LCO} predicted corrected for Hb = D_{LCO} predicted x (1.7Hb)/(9.38+Hb) **Percent predicted D_{LCO} corrected for Hb = [actual DLCO/ D_{LCO} predicted corrected for Hb] x 100%**
Rationale for change		Correction
Section to be changed		All sections in the protocol
Description of change		Editorial, grammatical updates
Rationale for change		Editorial, grammatical corrections throughout the document.

11.2 GLOBAL AMENDMENT 2

Date of amendment		18 Apr 2023
EudraCT number **EU number**		2020-005554-23
BI Trial number		1199-0378
BI Investigational Medicinal Product(s)		Ofev®, nintedanib
Title of protocol		An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 2 years, in children and

		adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Flow Chart – footnote 21 Bone imaging
Description of change		For new patients: Sentence adapted and sentences added: **Imaging follow-up will be conducted only in patients with open physes at predefined time points.** Imaging follow-up will be conducted, **if applicable,** at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks and every 24 weeks thereafter until the end of study or closure of the physes. **If it's not possible to conduct the follow-up at the predefined time points, the procedure can be done within 1 week before or after this time point with always minimum 10 weeks (first year)/22 weeks (thereafter) and always maximum 16 weeks (first year)/28 weeks (thereafter) from the previous procedure. Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.**
Rationale for change		Clarification and alignment of time window (with visit's time window)
Section to be changed		Flow Chart – footnote 21 Bone imaging
Description of change		For roll-over patients: Sentence adapted: ~~Within this timeframe, t~~Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.
Rationale for change		Clarification
Section to be changed		Flow Chart – footnote 21 Bone imaging
Description of change		For roll-over patients: Sentence added: **Preponement or postponement of one follow-up procedure within – 2 months to +2 months to the planned timepoint will be allowed once to align this procedure and the subsequent ones with the regular clinic visits planned in the protocol. After this alignment, the acceptable time window will be +/-1 week for this procedure**
Rationale for change		To align the schedule of safety procedures with patient's visit

Section to be changed		Flow Chart – footnote 21 Bone imaging
Description of change		For all patients: Sentence added: **For all patients, if the follow-up procedure cannot be conducted at least every 16 weeks (first year)/28 weeks (second year), the individual patient treatment needs to be interrupted upon discussion with the sponsor (except at the one time alignment with clinic visits mentioned above)**
Rationale for change		Clarification to be consistent with instructions mentioned in the appendice 10.9
Section to be changed		Flow Chart – footnote 22 clinical dental examination
Description of change		For new patients: Sentence adapted and sentences added: Follow-up will be conducted, **if applicable,** at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks and every 24 weeks thereafter until the end of the study. **If it's not possible to conduct the follow-up at the predefined time points, the procedure can be done within 1 week before or after this time point with always maximum 16 weeks (first year)/28 weeks (thereafter) from the previous procedure. Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.**
Rationale for change		Clarification and alignment of time window (with visit's time window)
Section to be changed		Flow Chart – footnote 22 clinical dental examination
Description of change		For roll-over patients: Sentence adapted: ~~Within this timeframe, t~~Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.
Rationale for change		Clarification
Section to be changed		Flow Chart – footnote 22 clinical dental examination
Description of change		For roll-over patients: Sentence added: **Preponement or postponement of one follow-up procedure within – 2 months to +2 months to the planned timepoint will be allowed once to align this procedure and the subsequent ones**

		with the regular clinic visits planned in the protocol. After this alignment, the acceptable time window will be +/-1 week for this procedure
Rationale for change		To align the schedule of safety procedures with patient's visit
Section to be changed		Flow Chart – footnote 22 clinical dental examination
Description of change		For all patients: Sentence added: **For all patients, if the follow-up procedure cannot be conducted at least every 16 weeks (first year)/28 weeks (second year), the individual patient treatment needs to be interrupted upon discussion with the sponsor (except at the one time alignment with clinic visits mentioned above)**
Rationale for change		Clarification to be consistent with instructions mentioned in the appendice 10.9
Section to be changed		Flow Chart – footnote 23 Dental imaging
Description of change		For new patients: Sentence adapted and sentences added: Follow-up will be conducted, **if applicable,** at 24 weeks, 52 weeks,104 weeks and every 48 weeks thereafter until the end of the study. **If it's not possible to conduct the follow-up at the predefined time points, the procedure can be done within 1 week before or after this time point with always minimum 22 weeks (first year)/46 weeks (thereafter) and always maximum 28 weeks (first year)/52 weeks (thereafter) from the previous procedure. Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.**
Rationale for change		Clarification and alignment of time window (with visit's time window)
Section to be changed		Flow Chart – footnote 23 Dental imaging
Description of change		For roll-over patients: Sentence adapted: ~~Within this timeframe, t~~Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.
Rationale for change		Clarification
Section to be changed		Flow Chart – footnote 23 Dental imaging
Description of change		For roll-over patients:

		Sentence added: **Preponement or postponement of one follow-up procedure within – 2 months to +2 months to the planned timepoint will be allowed once to align this procedure and the subsequent ones with the regular clinic visits planned in the protocol. After this alignment, the acceptable time window will be +/-1 week for this procedure**
Rationale for change		To align the schedule of safety procedures with patient's visit
Section to be changed		Flow Chart – footnote 23 Dental imaging
Description of change		For all patients: Sentence added: **For all patients, if the follow-up procedure cannot be conducted at least every 28 weeks (first year)/52 weeks (second year), the individual patient treatment needs to be interrupted upon discussion with the sponsor (except at the one time alignment with clinic visits mentioned above)**
Rationale for change		Clarification to be consistent with instructions mentioned in the appendice 10.9
Section to be changed		Flow Chart – footnote 24
Description of change		Sentence added: **Only one additional regular follow-up for bone imaging and for dental imaging procedures will be needed after the EOT visit if there is no pathological finding. If there is a pathological finding, follow-up procedures will be conducted on individual basis upon discussion with the sponsor and with the investigator. Follow –up procedures for clinical dental examination will be conducted as initially planned by the protocol.**
Rationale for change		To limit the burden for the patient while assuring patient safety
Section to be changed		Section 1.4.2 Risk - Table 1.4.2:1 Overview of trial related risks
Description of change		Sentence below adapted for "Impact on bone development and growth": The follow-up bone imagings will be planned, irrespective of scheduled visits, in order to respect the frequency of **around** every 12 weeks for first year and **around** every 24 weeks thereafter, taking in account, for roll-over patients, the participation

		in the parent trial.
Rationale for change		To be consistent with update in the flowchart footnote related to bone imaging procedures
Section to be changed		Section 1.4.2 Risk - Table 1.4.2:1 Overview of trial related risks
Description of change		Sentences below have been replaced for "Impact on dentition": The follow-up dental examinations will be planned, irrespective of scheduled visits, in order to respect the frequency of **around** every 12 weeks for first year and **around** every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial. … The follow-up dental imagings will be planned, irrespective of scheduled visits, in order to respect the frequency of **around** every 24 weeks for first year and **around** every 48 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial.
Rationale for change		To be consistent with the update of the flowchart footnotes related to clinical dental examination and to dental imaging procedure.
Section to be changed		Section 1.4.2 Risk - Table 1.4.2:1 Overview of trial related risks
Description of change		Sentences below have been adapted for "radiation exposure": **Bone** MRI/x-ray required with always minimum 10 weeks (first year)/22 weeks (thereafter) and dental X-ray required with always minimum 22 weeks (first year)/46 weeks (thereafter) ~~and always minimum 16 weeks (first year)/28 weeks (thereafter)~~ from the previous procedure, taking into account, for roll-over patients, the participation in the parent trial **(except at the one time alignment of these safety procedures with clinic visits)**. Similarly, **Bone** MRI/x-ray at EoT required only if previous MRI/x-ray not available within 12 weeks in the first year, 24 weeks thereafter. ~~Within this timeframe, t~~Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.
Rationale for change		Clarification and to be consistent with the update of the flowchart footnotes related to bone imaging and to dental imaging procedures.
Section to be changed		Section 2.2.2 further endpoints

Description of change		Further safety endpoint below updated: • Change in height~~, sitting height, leg length~~ from baseline at week 24, week 52, week 76, and week 104;
Rationale for change		Endpoints removed and data to be provided in listings due to inconsistent method of measurement impacting comparability of data
Section to be changed		Section 5.2.5 Assessment of pathological findings of epiphyseal growth plate
Description of change		Sentences below have been adapted: The follow-up will be planned, irrespective of scheduled visits, in order to respect the frequency of **around** every 12 weeks for first year and **around** every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial~~. If it is not possible to enduct the follow-up at the predefined time points, the procedure can be done within 2 weeks before or 4 weeks after this time point~~ with always minimum 10 weeks (first year)/22 weeks (thereafter) and always maximum 16 weeks (first year)/28 weeks (thereafter) from previous procedure. Please refer to Flow Chart footnotes for more details. ~~Within this timeframe, t~~Timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.
Rationale for change		To be consistent with the update of the flowchart footnotes related to bone imaging procedures.
Section to be changed		Section 5.2.6 Assessment of pathological on dental examination or imaging
Description of change		Sentences below have been adapted: Dental examination follow-ups will be planned, irrespective of scheduled visits, in order to respect the frequency of around every 12 weeks for first year and around every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial~~. If it is not possible to enduct the follow-up at the predefined time points, the procedure can be done within 2 weeks before or 4 weeks after this time point~~ with always maximum 16 weeks (first year)/28 weeks (thereafter) from previous procedure. Please refer to Flow Chart footnotes for more details. Within this timeframe, timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.

Rationale for change		To be consistent with the update of the flowchart footnotes related to clinical dental examination.
Section to be changed		Section 5.2.6 Assessment of pathological on dental examination or imaging
		Sentences below have been adapted: Dental imaging follow-ups will be planned, irrespective of scheduled visits, in order to respect the frequency of **around** every 24 weeks for first year and **around** every 48 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial~~. If it is not possible to enduct the follow-up at the predefined time points, the procedure can be done within 2 weeks before or 4 weeks after this time point~~ with always minimum 22 weeks (first year)/46 weeks (thereafter) and always maximum 28 weeks (first year)/52 weeks (thereafter) from previous procedure. Please refer to Flow Chart footnotes for more details. Within this timeframe, timepoints may be adapted on a case-by-case basis after discussion with the sponsor if appropriate for patient's safety.
Rationale for change		To be consistent with the update of the flowchart footnotes related to to dental imaging procedures.
Section to be changed		Section 6.2.2 Treatment period(s) – Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, X (treatment period)
Description of change		Sentences below have been adapted: Follow-up bone imaging (MRIs or x-rays if baseline MRI was not possible) will be planned, in order to follow the frequency of **around** every 12 weeks for first year and **around** every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial: •For new patients**,** imaging follow-up will be conducted, **if applicable,** at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks and every 24 weeks thereafter until the end of the study or closure of the physes. •For roll-over patients, imaging follow-up will be conducted **around** every 12 weeks in the following year after the MRI/x-ray considered as baseline for parent trial (when applicable) and **around** every 24 weeks thereafter until the end of the study or closure of the physes.
Rationale for change		To be consistent with the update of the flowchart footnotes related to bone imaging procedures.
Section to be changed		Section 6.2.2 Treatment period(s) – Visits 3, 4, 5,

		6, 7, 8, 9, 10, 11, X (treatment period)
Description of change		Sentences below have been adapted: Follow-up dental examination will be planned in order to follow the frequency of **around** every 12 weeks for first year and **around** every 24 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial: •For new patients**,** follow-up will be conducted, **if applicable,** at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks and every 24 weeks thereafter until the end of the study. •For roll-over patients, follow-up will be conducted **around** every 12 weeks in the following year after the dental examination considered as baseline in parent trial (when applicable) and **around** every 24 weeks thereafter until the end of the study.
Rationale for change		To be consistent with the update of the flowchart footnotes related to clinical dental examination.
Section to be changed		Section 6.2.2 Treatment period(s) – Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, X (treatment period)
Description of change		Sentences below have been adapted: Follow-up dental imaging will be planned in order to follow the frequency of **around** every 24 weeks for first year and **around** every 48 weeks thereafter, taking in account, for roll-over patients, the participation in the parent trial: •For new patients, follow-up will be conducted, **if applicable,** at 24 weeks, 52 weeks,104 weeks and every 48 weeks thereafter until the end of the study. •For roll-over patients, follow-up will be conducted, irrespective of scheduled visits, **around** every 24 weeks in the following year after the dental imaging considered as baseline for parent trial (when applicable) and **around** every 48 weeks thereafter until the end of the study.
Rationale for change		To be consistent with the update of the flowchart footnotes related to dental imaging procedures.
Section to be changed		Section 6.2.2 Treatment period(s) – **Patients who prematurely discontinued trial medication**
Description of change		At remaining scheduled visits, all procedures and assessments planned to be done under treatment need to be followed by the patient [redacted] The first visit after the EoT will be skipped if the

		EoT Visit occurs within 4 weeks prior to the scheduled visit but if MRI and/or dental examinations were planned at this visit, then they should be performed as planned. **Only one additional regular follow-up for bone imaging and for dental imaging procedures will be needed after the EOT visit if there is no pathological finding. If there is a pathological finding, follow-up procedures will be conducted on individual basis upon discussion with the sponsor and with the investigator. Follow –up procedures for clinical dental examination will be conducted as initially planned by the protocol.**
Rationale for change		To be consistent with the update of the flowchart footnotes related to bone imaging and dental imaging procedures.
Section to be changed		Section 10.9 Visit modification in exceptional circumstances – Table 10.9:1 Modification to visit procedures in exceptional circumstances
Description of change		Section related to follow-up monitoring of bone and teeth: Sentence adapted: 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 **(except at the one time alignment with clinic visits).**
Rationale for change		Clarification to be consistent with the update of the flowchart footnotes related to bone imaging and dental imaging procedures.

11.3 GLOBAL AMENDMENT 3

Date of amendment		29 Nov 2023
EudraCT number **EU number**		2020-005554-23
BI Trial number		1199-0378
BI Investigational Medicinal Product(s)		Ofev®, nintedanib
Title of protocol		An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 2 years, in children and adolescents with clinically significant fibrosing

		Interstitial Lung Disease (InPedILD®-ON)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Title page, Synopsis-Title
Description of change		An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least ~~2~~ **3** years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON)
Rationale for change		Change of study treatment duration by adding an additional year of study treatment
Section to be changed		Synopsis-Trial rationale and section 1.3 Rationale for performing the trial
Description of change		The rationale of this open label trial is to collect additional safety and efficacy data of nintedanib in children and adolescents with clinically significant fibrosing ILD for at least ~~2~~ **3** years (applies to patients rolling over from the parent trial) or until alternative treatment options become available or are made available (e.g., via marketing authorization, via compassionate use or via similar process) (applies to new patients and to roll-over patients after ~~2~~ **3** years).
Rationale for change		Change of study treatment duration by adding an additional year of study treatment
Section to be changed		Synopsis –Duration of treatment
Description of change		Treatment duration for each patient will be variable. For roll-over patients: at least ~~2~~ **3** years~~; variable treatment duration afterwards,~~ **or** until alternative treatment options become or are made available (e.g., via marketing authorization, via compassionate use, or via similar process) to the patient outside of the clinical trial.
Rationale for change		Change of study treatment duration by adding an additional year of study treatment and simplification of the sentence
Section to be changed		Synopsis –Duration of treatment
Description of change		Treatment duration for each patient will be variable. … For new patients: until the overall end of the trial (with expected minimum treatment duration of ~~24~~ **76** weeks) ~~or, if earlier, until alternative treatment options become or are made available (e.g. via~~

		~~marketing authorization, via compassionate use, or via similar process) to the patient outside of the clinical trial~~.
Rationale for change		To increase the collection of long-term data
Section to be changed		Synopsis –Duration of treatment
Description of change		Sentences added: **Exception: patients aged 21 years must complete the trial before their 22nd birthday. Consequently, a treatment duration of at least 3 years might not be reached by some patients aged 21.**
Rationale for change		After longterm follow-up adult patients of 21 years should leave the trial.These patients should be able to have nintedanib available outside the study.
Section to be changed		Synopsis –Duration of treatment and section 3.1 Overall trial design
Description of change		The overall end of trial will take place approximately when last roll-over patient **still on-treatment** reaches **3** ~~2~~ years of treatment [redacted]**)** ensuring that nintedanib or alternative treatment options (e.g., via marketing authorization, via compassionate use, or via similar process) will be available for all remaining patients (roll-over or new patients) outside the trial at this time [redacted].
Rationale for change		Change of study treatment duration by adding an additional year of study treatment and clarification added for last roll-over patient
Section to be changed		Flow Chart
Description of change		Additional visits added related to additional year: **V12 to V15**
Rationale for change		Change of study treatment duration by adding an additional year of study treatment
Section to be changed		Flow Chart
Description of change		Additional information collected mentioned in the flow chart: [redacted]
Rationale for change		To collect with minor burden [redacted]
Section to be changed		Flow Chart - Bone imaging
Description of change		Information updated: On regular basis (Q12W to **Q48W**~~Q24W~~)
Rationale for change		Safety procedure only needed yearly for patients aged 19 or older.
Section to be changed		Flow Chart

Description of change		Additional information collected mentioned in the flow chart: Concomitant medication [redacted]
Rationale for change		[redacted]
Section to be changed		
Description of change		
Rationale for change		Change of study treatment duration
Section to be changed		Flow Chart
Description of change		[redacted]
Rationale for change		Change of study treatment duration
Section to be changed		Flow Chart –footnote 3
Description of change		Sentence updated: - Additional visits/ **Phone calls (if appropriate)** have to be included, in case of dose change (reduction or re-escalation) or in case of capsule's size change. Please refer to Section 6.2.2.
Rationale for change		To avoid patient to travel if not needed
Section to be changed		Flow Chart –footnote 3
Description of change		Sentence added: - **Patients aged 21 years must complete the trial while being 21 years old. They should perform EoT visit and EoS visit (28 days after) before their 22nd birthday.**
Rationale for change		After longterm follow-up adult patients of 21 years should leave the trial.These patients should be able to have nintedanib available outside the study.
Section to be changed		Flow Chart –footnote 16
Description of change		[redacted]
Rationale for change		Change of study treatment duration
Section to be changed		Flow Chart –footnote 21
Description of change		Sentence added: **For patients aged 19 and older, please see additional information at the end of the footnote.**
Rationale for change		Safety procedure only needed yearly for patients aged 19 or older.
Section to be changed		Flow Chart –footnote 21
Description of change		Sentences adapted:

		For new patients: … Imaging follow-up will be conducted, if applicable, at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks, **128 weeks, 156 weeks,** and every 24 weeks thereafter until the end of study or closure of the physes. …. **For all patients,** if the follow-up procedure cannot be conducted at least every 16 weeks (during the first year)/28 weeks (~~second year~~ **thereafter**), the study treatment of this individual patient needs to be interrupted upon discussion with the sponsor (except for the one-time alignment with clinic visits mentioned above for roll-over patients).
Rationale for change		Change of study treatment duration by adding an additional year of study treatment
Section to be changed		Flow Chart –footnote 21, section 5.2.5, Section 6.2.2 Treatment period(s) – follow-up bone imaging
Description of change		Sentence added: **For patients aged 19 and older, bone imaging follow-up procedures will be performed around every 48 weeks (instead of around every 24 weeks) until the end of the study or closure of the physes.**
Rationale for change		Safety procedure only needed yearly for patients aged 19 or older.
Section to be changed		Flow Chart –footnote 21,
Description of change		Paragraph reviewed to be clearer without adding any additional change than those previously mentioned
Rationale for change		Clarifications
Section to be changed		Flow Chart –footnote 22
Description of change		Sentences adapted: **For new patients:** … Follow-up will be conducted, if applicable, at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks, **128 weeks, 156 weeks,** and every 24 weeks thereafter until the end of study or closure of the physes. …. **For all patients,** if the follow-up procedure cannot

		be conducted at least every 16 weeks (during the first year)/28 weeks (~~second year~~ **thereafter**), the study treatment of this individual patient needs to be interrupted upon discussion with the sponsor (except for the one-time alignment with clinic visits mentioned above for roll-over patients).
Rationale for change		Change of study treatment duration by adding an additional year of study treatment
Section to be changed		Flow Chart –footnote 22
Description of change		Paragraph reviewed to be clearer without adding any additional change than those previously mentioned
Rationale for change		Clarifications
Section to be changed		Flow Chart –footnote 23
Description of change		Sentences adapted: **For new patients:** … Follow-up will be conducted, if applicable, at 24 weeks, 52 weeks,104 weeks, **156 weeks**, and every 48 weeks thereafter until the end of the study. …. **For all patients,** if the follow-up procedure cannot be conducted at least every 16 weeks (during the first year)/28 weeks (~~second year~~ **thereafter**), the study treatment of this individual patient needs to be interrupted upon discussion with the sponsor (except for the one-time alignment with clinic visits mentioned above for roll-over patients).
Rationale for change		Change of study treatment duration by adding an additional year of study treatment
Section to be changed		Flow Chart –footnote 23
Description of change		Paragraph reviewed to be clearer without adding any additional change than those previously mentioned
Rationale for change		Clarifications
Section to be changed		Flow Chart –footnote 24
Description of change		2 sentences removed according to flow chart update: At the EoT visit: [redacted]

		[redacted] • the MRI/x-ray should not be repeated if the last MRI/x-ray was conducted within 24 weeks, • the dental examination will not be repeated if the last examination was conducted within 12 weeks and • the dental imaging will not be repeated if the last examination was conducted within 24 weeks.
Rationale for change		Procedures to be always done at EOT following change of study duration
Section to be changed		Flow Chart –footnote 24
Description of change		If EoT occurs before Visit **15** ~~11~~ (week **156** ~~104~~), roll-over patients will be asked to remain in the study and to return to all regularly scheduled visits until week**156** ~~104~~.
Rationale for change		Change of study treatment duration
Section to be changed		Flow Chart –footnote 24
Description of change		New patients who prematurely discontinued trial drug will be asked to remain in the study and to return to all regularly scheduled visits until the overall end of trial or, ~~if earlier, until alternative treatment options become or are made available to the patient outside the clinical trial~~.
Rationale for change		To increase the collection of long-term data
Section to be changed		Flow Chart –footnote 25
Description of change		For patients who discontinue trial treatment prematurely and are not able to complete the scheduled visits, a follow-up (FU) visit should be planned 28 days after EoT. In addition, every attempt will be made to get information on vital status, when applicable, at 24 ~~weeks~~, 52 ~~weeks~~, 76 ~~weeks~~, 104 ~~weeks~~, **128, 156, and every 24 weeks thereafter until the end of the study** and for new patients at EoS. Please see Section 5.2.7.2.1
Rationale for change		Change of study treatment duration
Section to be changed		Flow Chart –footnote 28
Description of change		For patients who discontinue permanently trial treatment before Visit **15** ~~11~~ and who accepted to attend further scheduled visits as per protocol, then the patient's trial completion will be at initial planned date of Visit **15** ~~11~~ (at week **156** ~~104~~) for roll-over patients and at the overall end of trial ~~or,~~

		~~if earlier, when treatment options become or are made available for new patients~~.
Rationale for change		Change of study treatment duration and to increase the collection of long-term data
Section to be changed		Flow Chart – footnote 30
Description of change		footnote 30 added: [redacted]
Rationale for change		To collect with minor burden a [redacted]
Section to be changed		Section 1.3 Rationale of the trial
Description of change		It is expected that availability of nintedanib via marketing authorization, or via compassionate use or via similar process, as offered/provided by the sponsor (depending on local laws) occurs approximately ~~when last roll-over patient reaches 3 years of treatment [redacted])~~. **However, roll-over patients should stay in the trial for at least 3 years and new patients should stay in the trial until the end of (with the exception of patients ≥ 22 years of age) to ensure collection of patient data for a prolonged period of time.**
Rationale for change		Study prolongation
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		Clarification

Section to be changed		Section 3.1 Overall trial design
Description of change		Trial design graph updated to reflect the increase of treatment duration
Rationale for change		Study treatment prolongation
Section to be changed		Section 3.1 Overall trial design
Description of change		Roll-over patients will be requested to stay in the trial for at least **156** ~~104~~ weeks (until **Visit 15** ~~11~~). At week 156, roll-over patients who can be treated with nintedanib or alternative treatment options outside the clinical trial will have their EoT Visit instead of Visit **15** ~~11~~).
Rationale for change		Study treatment prolongation
Section to be changed		Section 3.1 Overall trial design
Description of change		New patients will **be requested** to stay in the trial until the end of trial (with expected minimum treatment duration of **76** ~~24~~ weeks) ~~or, if earlier, until alternative treatment options become or are made available (e.g. via marketing authorization, via compassionate use, or via similar process) to the patient outside the trial.~~ ~~When nintedanib or alternative treatment options become or are made available for patients outside the trial~~, **then** patients will perform their EoT Visit and enter in the 28-days follow-up period off-treatment until End of Study Visit (EOS).
Rationale for change		Change of study treatment duration and to increase the collection of long-term data
Section to be changed		Section 3.1 Overall trial design
Description of change		**Exception: patients aged 21 years must complete the trial before their 22nd birthday. Consequently, a treatment duration of at least 3 years might not be reached for by patients aged 21.** **Patients completing trial while being 21 years old, even with a treatment duration less than 3 years, will be considered as completed patients.**
Rationale for change		After longterm follow-up adult patients of 21 years should leave the trial.These patients should be able to have nintedanib available outside the study.
Section to be changed		Section 3.1 Overall trial design
Description of change		At this time, all the remaining patients will perform their EoT Visit. For logistical reasons, it may be planned that EoT visit of all remaining patients will occur within 6 weeks before the latest Visit **15** ~~11~~ of roll-over patients. If regular scheduled visit is planned for a

		patient during this period of 6 weeks, then the patient will skip this regular visit and will perform directly the EoT visit instead. After the EoT visit, all remaining patients will enter a 4-week follow-up period.
Rationale for change		Study treatment prolongation
Section to be changed		Section 3.1 Overall trial design
Description of change		Roll-over patients will be considered as prematurely discontinued from trial treatment if they stop trial medication before week **156** ~~104~~ **(except at the age of 21)** ~~**or if they stop trial medication after week 104 but without any other treatment option available.**~~ New patients will be considered as prematurely discontinued from trial treatment if they discontinue trial treatment before ~~nintedanib or alternative treatment options are available outside the clinical trial~~ **the overall end of trial (except at the age of 21).**
Rationale for change		Study treatment prolongation, change for patients aged 21 years old and change to increase the collection of long-term data
Section to be changed		Section 3.1 Overall trial design
Description of change		Roll-over patients prematurely discontinued from trial treatment before week **156** ~~104~~ will be asked to remain in the study and return to all regularly scheduled visits until Visit **15** ~~11~~ (individual planned date of week **156** ~~104~~). New patients prematurely discontinued from trial treatment will be asked to remain in the study until the overall end of trial (expected to occur approximately when last roll-over patient **still on-treatment** reaches **3** ~~**2**~~ years of treatment) ~~or, if earlier, until alternative treatment options become available~~.
Rationale for change		Study treatment prolongation and change to increase the collection of long-term data
Section to be changed		Section 3.1 Overall trial design
Description of change		For patients who prematurely discontinued trial drug and who are unable to complete the scheduled visits, a follow-up (FU) visit should be planned for 28 days after EoT. In addition, every attempt will be made to collect information on vital status, when applicable, at weeks 24, 52, 76, 104, **128 and 156** and for new patients at EoS.
Rationale for change		Study treatment prolongation

Section to be changed		Section 3.1 Overall trial design and Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Description of change		Sentence removed: ~~For new patients who prematurely discontinued trial drug, if nintedanib or alternative treatment options become or are made available outside the clinical trial before the overall end of trial, then vital status will be collected for the last time at that time and this will define the end of patient's participation in the trial (trial completion).~~
Rationale for change		To increase the collection of long-term data
Section to be changed		Section 3.1 Overall trial design and Section 3.3.4.1 Discontinuation of trial treatment and Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Sentence added: **If it is intended by a treatment discontinued patient to use available nintedanib outside the trial after trial treatment discontinuation, the patient should directly undergo the EoS visit 28 days after the EOT visit (no vital status will be required for this patient).**
Rationale for change		Clarification
Section to be changed		Section 3.3.4 Discontinuation of patients from treatment or assessments
Description of change		However, if the patients agree, they should stay in the trial even if continued trial treatment is not possible: roll-over patients should attend further trial visits until Visit **15** ~~**11**~~ and new patients should attend until the overall end of trial ~~or, if earlier, until treatment options become or are made available~~ to ensure their safety and to collect important trial data.
Rationale for change		Study treatment prolongation and to increase the collection of long-term data
Section to be changed		Section 3.3.4.1 Discontinuation of trial treatment
Description of change		The patient can no longer receive trial treatment for medical reasons such, adverse events, other diseases, or pregnancy. If a patient becomes pregnant during the trial the investigational product must be **interrupted** ~~discontinued~~ immediately, and the patient will be followed up until birth of the child/children or otherwise termination of the pregnancy. **The study medication may be only re-introduced once the**

		child has been born and the mother is no longer nursing, if supported by individual benefit risk as judged by the investigator.
Rationale for change		To give patients the possibility to restart trial treatment after pregnancy
Section to be changed		Section 3.3.4.1 Discontinuation of trial treatment
Description of change		In case of permanent 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 planned observation period. For those patients who are unable to complete the remaining scheduled visits, every attempt will be made to get information on vital status ~~every 24 weeks after Visit 2 until the individual planned observation period of 104 weeks~~ as outlined in the Flow Chart and Section 6.2.3.
Rationale for change		Study treatment prolongation
Section to be changed		Section 3.3.4.1 Discontinuation of trial treatment
Description of change		Sentence added: **If it is intended by the patient to use commercial nintedanib after trial treatment discontinuation, the patient should directly undergo the EoS visit 28 days after the EOT visit.**
Rationale for change		Clarification
Section to be changed		Section 4.1.4 Drug assignment and administration of dose for each patient - Section 6.2.2 Treatment period(s) - Dose reduction visit / dose increase visit/ Change of capsule size visit
Description of change		Sentence added: **In case the start/end of an AE requires a dose reduction/increase without the need of a change in capsule size and without requiring a meeting with the investigator in person, the unscheduled visit for the patient can be replaced by a phone call. The investigator will register the phone call in IRT as an unscheduled visit and register the dose reduction/increase on the respective page in the eCRF.**
Rationale for change		To avoid patient to travel if not needed
Section to be changed		Section 4.2.1 Other treatments and emergency procedures
Description of change		Sentence added: [redacted]

		during the trial will be recorded in the eCRF.
Rationale for change		[redacted]
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Sentence added: The use of nintedanib other than the investigational product is prohibited throughout the study, including the follow-up period (if any). **If it is intended by the patient to use commercial nintedanib after trial treatment discontinuation, the patient should directly undergo the EoS visit 28 days after the EOT visit.**
Rationale for change		Clarification
Section to be changed		[redacted]
Description of change		Physician reported Fan severity score [R09-5337] at Visit 2 will be used to determine eligibility of new patient. [redacted] For instructions on how to assign the severity-of-illness score see Appendix 10.2
Rationale for change		[redacted]
Section to be changed		Section 6.2.1 Screening and run-in period(s) - Visit 1 (Screening) for new patients
Description of change		• Medical history including pre-existing conditions **(including** [redacted] **if applicable)** will be recorded. • Concomitant therapy including previous medications [redacted] will be recorded
Rationale for change		To reflect the update of the flow chart
Section to be changed		Section 6.2.2 Treatment period(s) – Visit 1/Visit 2 for roll-over patients
Description of change		Sentence updated: Baseline Conditions/Medical History: • Medical history including pre-existing conditions **(including** [redacted] **if applicable)** will be recorded. Concomitant therapy including previous medications [redacted] will be recorded.

Rationale for change		To reflect the update of the flow chart
Section to be changed		Section 6.2.2 Treatment period(s) –Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, X (treatment period)
Description of change		Sentence adapted: Additional clinic visits will be scheduled ~~after 12, 24, 36, 52, 64, 76, 88 and 104 weeks of treatment (Visits 4 to 11) and when applicable, every 12 weeks (Visit X) thereafter~~ **on regular basis from Visit 2 until End of Treatment (EOT) visit.** Detailed procedures and assessment to be performed at each Visit are described in Flow Chart and Section 5. Sentence added: **As the treatment duration for each patient will be variable, some visits may not apply (to some new patients and to some patients aged 21)**
Rationale for change		Study treatment prolongation, change for patients aged 21 years old and clarification
Section to be changed		Section 6.2.2 Treatment period(s) - Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, X (treatment period)
Description of change		**Visits 12 to 15 added** in the description of procedures during treatment period
Rationale for change		Study treatment prolongation
Section to be changed		Section 6.2.2 Treatment period(s) – Visit 2 for new patients – and Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, X (treatment period) and Dose reduction visit / dose increase visit/ Change of capsule size visit
Description of change		Sentence updated: Adverse events [redacted] ~~and~~ concomitant therapy [redacted] since last visit will be reviewed and recorded
Rationale for change		To reflect the update of the flow chart
Section to be changed		Section 6.2.2 Treatment period(s) – follow-up bone imaging
Description of change		Sentence updated: •**For new patients,** follow-up will be conducted, if applicable, at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks, **128 weeks, 156 weeks,** and every 24 weeks thereafter until the end of the study.
Rationale for change		Study treatment prolongation

Section to be changed		Section 6.2.2 Treatment period(s) – follow-up dental examination
Description of change		Sentence updated: **For new patients,** follow-up will be conducted, if applicable, at 12 weeks, 24 weeks, 36 weeks, 52 weeks, 76 weeks, 104 weeks, **128 weeks, 156 weeks,** and every 24 weeks thereafter until the end of the study.
Rationale for change		Study treatment prolongation
Section to be changed		Section 6.2.2 Treatment period(s) – follow-up dental imaging
Description of change		•**For new patients,** follow-up will be conducted, if applicable, at 24 weeks, 52 weeks,104 weeks, **156 weeks,** and every 48 weeks thereafter until the end of the study.
Rationale for change		Study treatment prolongation
Section to be changed		Section 6.2.2 Treatment period(s) - treatment period duration
Description of change		Treatment duration for each patient will be variable. Roll-over patients will be requested to stay in the trial for at least **156** ~~104~~ weeks (until Visit **15** ~~11~~). At week **156** ~~104~~, roll-over patients who can be treated with nintedanib or alternative treatment options outside the clinical trial will have their EoT Visit. The remaining roll-over patients will continue in the trial until nintedanib, or alternative treatment options become available to them outside the clinical trial. Trial treatment will be stopped prematurely if a reason for withdrawal is met (refer to Section 3.3.4). After week **156** ~~104~~, if reason for study treatment discontinuation is that nintedanib or alternative treatment options become available for patient outside the clinical trial, then the patient will not be considered as early discontinued for treatment.
Rationale for change		Study treatment prolongation
Section to be changed		Section 6.2.2 Treatment period(s) - treatment period duration
Description of change		New patients will stay in the trial until the overall end of the trial (with expected minimum treatment duration of **76** ~~24~~ weeks) ~~or, if earlier, until alternative treatment options become or are made~~

		~~available (e.g. via marketing authorization, via compassionate use, or via similar process) to the patient outside of the clinical trial,~~ then patients will perform the EoT Visit.
Rationale for change		Study treatment prolongation and change to increase the collection of long-term data
Section to be changed		Section 6.2.2 Treatment period(s) – End of Treatment Visit
Description of change		Sentence removed as repetition: ~~Patients who discontinued trial treatment prematurely will undergo the EoT visit as soon as possible.~~ Sentence adapted for clarification: If a patient discontinues the study during a scheduled treatment visit, then the scheduled visit will be ~~considered as an~~ **replaced by the** EoT visit.
Rationale for change		Clarification
Section to be changed		Section 6.2.2 Treatment period(s) – End of Treatment Visit
Description of change		Sentence updated: As consequence, roll-over patients that discontinue trial treatment at week **156** ~~**104**~~ should perform EoT visit instead of Visit **15** ~~**11**~~.
Rationale for change		Study treatment prolongation
Section to be changed		Section 6.2.2 Treatment period(s) – End of Treatment Visit
Description of change		Observation and procedures updated as follow: • [redacted] • Adverse events, [redacted] ~~and~~ [redacted] since last visit will be reviewed and recorded Added: • [redacted] • [redacted] **if applicable and if not collected before.**
Rationale for change		To reflect the update of the flow chart

Rationale for change		Section 6.2.2 Treatment period(s) – End of Treatment Visit
Section to be changed		Sentence added: **Exception: patients aged 21 years must complete the trial before their 22nd birthday. The EoT visit followed by EoS visit must be performed before the 22nd birthday.**
Description of change		After longterm follow-up adult patients of 21 years should leave the trial.These patients should be able to have nintedanib available outside the study.
Rationale for change		Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Section to be changed		Sentence added: **Exception: patients aged 21 years must complete the trial before their 22nd birthday. Remaining scheduled visits or vital status will be replaced by the EoS visit which must be performed before the 22nd birthday.**
Description of change		After longterm follow-up adult patients of 21 years should leave the trial.These patients should be able to have nintedanib available outside the study.
Section to be changed		Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Description of change		Roll-over patients who discontinued trial treatment prematurely before week156, patient will be asked to remain in the study and to return to remaining scheduled visits until the initial planned week **156** ~~104~~ (Visit **15** ~~11~~) New patients who discontinued treatment prematurely will be asked to remain in the study and to return to remaining scheduled visits until the overall end of trial ~~or, if earlier, until alternative treatment options become or are made available.~~
Rationale for change		Study treatment prolongation and change to increase the collection of long-term data
Section to be changed		Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Description of change		The last visit to be performed by prematurely discontinued roll-over patients will be the Visit **15** ~~11~~ including trial completion and the last visit to be performed by new patients prematurely discontinued will be EoS including trial completion. If patients are not able to complete the remaining

		scheduled visits, a follow-up (FU) visit should be planned for 28 days after EoT. In addition, every attempt will be made to get information on vital status, when applicable, at 24 weeks, 52 weeks, 76 weeks and 104 weeks, **128 weeks, 156 weeks**, and for new patients at EoS.
Rationale for change		Study treatment prolongation
Section to be changed		Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Description of change		Sentence added: **Additionally, for treatment discontinued patients, if it is intended by the patient to use commercial nintedanib after trial treatment discontinuation, the patient should directly undergo the EoS visit 28 days after the EOT visit.**
Rationale for change		Clarification
Section to be changed		Section 6.2.2 Treatment period(s) – Patients who prematurely discontinued trial medication
Description of change		Sentence removed: ~~For roll-over patients who discontinued trial treatment prematurely after week 156 104 but before alternative treatment options become or are made available, a FU visit should be planned for 28 days after EoT. This will be the last visit for the patient.~~ ~~For roll-over patients who discontinued trial treatment prematurely after week 104 but before alternative treatment options become or are made available, a FU visit should be planned for 28 days after EoT. This will be the last visit for the patient.~~
Rationale for change		Patients can directly do the EoS visit
Section to be changed		Section 6.2.2 Treatment period(s) – Follow-up visit
Description of change		Sentence added: **F-up visit should be conducted 28 days (+7 days) after the EoT visit for all discontinued patients who are able to complete the remaining visits or who accepted the vital status collection.**
Rationale for change		Clarification
Section to be changed		Section 6.2.3 Follow-up and trial completion End of Study Visit - End of Study visit
Description of change		EoS visit should be conducted 28 days (+7 days) after the EoT visit for all patients **except discontinued patients who are able to complete the remaining visits or who accepted the vital**

		status collection ~~who didn't prematurely discontinue trial treatment~~.
Rationale for change		Clarification
Section to be changed		Section 6.2.3 Follow-up and trial completion - End of Study visit
Description of change		Sentence updated: • Adverse events, [redacted] concomitant therapy [redacted] since last visit will be reviewed and recorded. Sentence updated: • [redacted] **if applicable and if not collected before.**
Rationale for change		To reflect the update of the flow chart
Section to be changed		Section 6.2.3 Trial completion
Description of change		Update and clarification: **The trial completion CRF page must be filled-in when the patient has terminated the trial.** The trial completion (individual patient's end of trial) is: • At the end of the EoS Visit for patients who have completed the trial on treatment as planned **(including patients aged 21)**. • At week **156** ~~104~~, for roll-over patients who prematurely discontinued trial treatment before Visit **15** ~~11~~ and were able to stay in the trial until week **156** ~~104~~. • At the **overall** end of the **trial** ~~EoS Visit~~ for new patients who prematurely discontinued trial treatment and were able to stay in the trial until the overall end of trial ~~or, if earlier, until alternative treatment options become or are made available~~. • At F-up/**EoS** visit, for roll-over patients who prematurely discontinued trial treatment before Visit **15** ~~11~~ and were not able to stay in the trial until week **156** ~~104~~ ~~or who prematurely discontinued trial treatment after week~~ **~~156 104~~** and for new patients who prematurely discontinued trial treatment and were not able to stay in the trial until the overall end of trial ~~or, if earlier, until alternative treatment options become available.~~ • At last contact, for other cases.
Rationale for change		Update and clarification needed following other

		changes previously introduced
Section to be changed		Section 8 infromed consent, trial records, data protection, publication policy, and administrative structure
Description of change		The trial will be carried out in accordance with the ~~Medical Devices Directive (93/42/EEC)~~ Medical Device Regulation (EU) 2017 / 745 and the harmonised standards for Medical Devices (ISO 14155, current version).
Rationale for change		Change in regulation

11.4 GLOBAL AMENDMENT 4

Date of amendment		15 Apr 2024
EudraCT number **EU number**		2020-005554-23
BI Trial number		1199-0378
BI Investigational Medicinal Product(s)		Ofev®, nintedanib
Title of protocol		An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Title page
Description of change		The Universal Trial Number (UTN) was added
Rationale for change		Updated information.
Section to be changed		Clinical protocol synospsis, section 3.3.2. Inclusion criteria, section 3.3.3. Exclusion criteria
Description of change		Trial population in France is limited to adolescents 12 to 17 years old at Visit 2.
Rationale for change		Harmonisation of the CTP for the transition to EU Clinical Trials Regulation with inclusion of current Local Amendment 1 France requested by French Health Authority (ANSM) and already approved to limit the age groups to be enrolled in France.
Section to be changed		Flowchart footnote 13, Section 1.4.2. Table 1.4.2:1 overview of trial related risks, Section 5.2.3. Safety laboratory parameters, Section 6.2.2. treatment period(s), Section 10.9 Visit modification in exceptional circumstances– Table 10.9:1 Modification to visit procedures in exceptional

		circumstances
Description of change		Pregnancy testing will be done every 4 weeks for female patients in Poland and in Norway.
Rationale for change		Harmonisation of the CTP for the transition to EU Clinical Trials Regulation with inclusion of current Local Amendment 1 Poland (requested by Polish Authorities and already approved) and current local amendment 1 Norway (requested by the Norvegian Medecines Agency and already approved).
Section to be changed		Flow Chart:V3a and footnote 4
Description of change		For new patients in Norway, the Visit 3a is also applicable and should be performed at Week 6 (Day 43).
Rationale for change		Harmonisation of the CTP for the transition to EU Clinical Trials Regulation with inclusion of current Local Amendment 1 Norway requested and already approved by the Norvegian Medecines Agency.
Section to be changed		Flow Chart V12 - End of study
Description of change		V12 should be performed at Day **813** +/- 7 days V13 should be performed at Day **897** +/- 7 days V14 should be performed at Day **981** +/- 7 days V15 should be performed at Day **1093** +/- 7 days VX should be performed at Day **1093**+Q84 with time window of +/- 7 days
Rationale for change		Correction of calculation (1 day was missing)
Section to be changed		Flow chart – footnote 25 and Section 6.2.2 treament period(s) – follow-up visit
Description of change		Sentences added: **If the EoT visit has been delayed and has been done 28 days or more after the treatment discontinuation, the follow-up (FU) visit can be skipped.**
Rationale for change		To limit the burden for the patient
Section to be changed		Flow chart – footnote 26 and Section 6.2.3 Follow-up and trial completion - End of Study visit
Description of change		Sentences added: **In exceptional cases, when the patient is not able to come at site for medical reason, the EoS visit can be replaced by a phone call. If the EoT visit has been delayed and has been done 28 days or more after the treatment discontinuation, the EoS visit can be skipped.**
Rationale for change		To limit the burden for the patient.
Section to be changed		Flow chart – footnote 28

Description of change		For patients who discontinue permanently trial treatment before Visit 15 and who accepted to attend further scheduled visits as per protocol, then the patient's trial completion will be at initial planned date of Visit 15 (at week 156) for roll-over patients and at the overall end of trial ~~**or, if earlier, when treatment options become or are made available**~~ for new patients**.**
Rationale for change		Correction following previous CTP revision
Section to be changed		Flow chart – footnote 28
Description of change		Sentence added: **Completion of trial participation will be conducted at EoT visit, if FU/EoS visit is skipped due to delayed EoT for more than 28 days.**
Rationale for change		To limit the burden for the patient
Section to be changed		Section 6.2.2 treament period(s) –follow-up visit
Description of change		Sentence corrected: F-up visit should be conducted 28 days (+7 days) after the EoT visit for all discontinued patients who are **not** able to complete the remaining visits or who accepted the vital status collection.
Rationale for change		Correction
Section to be changed		Section 6.2.3 Follow-up period and trial completion – End of study visit
Description of change		Sentence updated: EoS visit should be conducted 28 days (+7 days) after the EoT visit for **patients who have completed the trial on treatment as planned** ~~**all patients except discontinued patients who are able to complete the remaining visits or who accepted the vital status collection**~~. …. Sentence added: **The EoS should be conducted at week 156 for prematurely discontinued roll-over patients who were able to complete the remaining visits off-treatment until week 156 and at the overall end of the trial for new patients who prematurely discontinued trial treatment and were able to stay in the trial until the overall end of trial.**
Rationale for change		clarification
Section to be changed		Section 11.3 Global Amendment 3 description of change- change in section 3.1 (page 190)
Description of change		Roll-over patients will be considered as

		prematurely discontinued from trial treatment if they stop trial medication before week 156 (except at the age of 21) ~~**or if they stop trial medication after week 104 but without any other treatment option available.**~~
Rationale for change		Correction in the description of the change

11.5 GLOBAL AMENDMENT 5

Date of amendment		27 Nov 2024
EU Clinical Trial No		2024-515743-27-00
BI Trial number		1199-0378
BI Investigational Medicinal Product(s)		Ofev®, nintedanib
Title of protocol		An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Title page
Description of change		The EU Clinical Trial Number was added
Rationale for change		Updated information.
Section to be changed		Synopsis –Duration of treatment
Description of change		The overall end of trial will take place approximately when last roll-over patient ~~still on treatment~~ **is expected to reach** ~~reaches~~ 3 years of treatment ([redacted]) ensuring that nintedanib or alternative treatment options (e.g., via marketing authorization, via compassionate use, or via similar process) will be available for all remaining patients (roll-over or new patients) outside the trial at this time.
Rationale for change		Clarification to avoid changing the timelines of overall end of trial in the last months of the study. In addition, as patients may travel long distances to expert centers, longer term planning needs to occur.
Section to be changed		Flow Chart - footnote 3, Section 4.2.1.2 Management of liver enzymes elevations, Table 4.2.1.2:1 Recommendations for managing liver enzyme elevations - footnote 4, Section 4.2.2.1. Restrictions regarding concomitant treatment,

		Section 5.2.3 Safety laboratory parameters –'a-Visits' section, Section 6.2.2. Intermediate "a-Visits"
Description of change		Sentences adapted to clarify that the specific lab kit (visit-a) should be preferably used to monitor hepatic parameters, but local lab will be also acceptable.
Rationale for change		Clarification to limit the burden for the patient enable timely availability of safety lab and to give flexibility
Section to be changed		Flowchart – footnote 13, Section 1.4.2. Risks – table 1.4.2:1 Overview of trial related risks – Feotal harm, Section 5.2.3 Safety laboratory parameters – Pregnancy tests and Table 5.2.3:1 Safety laboratory tests at scheduled site visits, Section 6.2.2. other observations and procedures, Section 6.2.2. Intermediate pregnancy tests, Section 6.2.2. End of Treatment Visit, Section 6.2.2. Patients who prematurely discontinued trial treatment, section, Section 10.9 Visit modification in exceptional circumstances– Table 10.9:1 Modification to visit procedures in exceptional circumstances
Description of change		frequency of pregnancy testing harmonised: every 4-6 weeks (with every 4 weeks for female patients in Poland and Norway) Changed for all countries to: every **4 weeks**.
Rationale for change		Harmonisation requested by Italian H.A. following transition to new regulation in Europe
Section to be changed		Flowchart – footnote 24 and section 6.2.2. Treatment period(s) - Patient who prematurely discontinued trial medication
Description of change		One sentence adapted to clarify that at remaining visits off-treatment visits, IRT call/notification is not needed anymore
Rationale for change		Clarification
Section to be changed		Flowchart –footnote 13 and footnote 24 and section 6.2.2. Treatment period(s) - Patient who prematurely discontinued trial medication
Description of change		In case of treatment discontinuation when a female patient continues with visits off treatment, then the urine pregnancy tests at home are only required to be continued every 4 weeks for the 3 months after last trial drug intake.

Rationale for change		To limit the burden of the patient.
Section to be changed		[redacted]
Description of change		
Rationale for change		Change following authorities' interactions
Section to be changed		section 3.1 Overall trial design
Description of change		The overall end of trial will take place approximately when last roll-over patient ~~still on treatment~~ **is expected to reach** ~~reaches~~ 3 years of treatment [redacted]) ensuring that nintedanib or alternative treatment options (e.g., via marketing authorization, via compassionate use, or via similar process) will be available for all remaining patients (roll-over or new patients) outside the trial at this time. At this time, all the remaining patients will perform their EoT Visit. For logistical reasons, it may be planned that EoT visit of all remaining patients will occur within 6 weeks before the **planned date of** ~~**latest**~~ Visit 15 of **last** roll-over patient. … New patients prematurely discontinued from trial treatment will be asked to remain in the study until the overall end of trial (expected to occur approximately when last roll-over patient ~~still on treatment~~ **is expected to reach** ~~reaches~~ 3 years of treatment).
Rationale for change		Clarification

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Reason for signing: Approved	[redacted] Date of signature: 29-Nov-2024 08:11:41 GMT+0000
Reason for signing: Approved	[redacted] Date of signature: 29-Nov-2024 08:16:16 GMT+0000
Reason for signing: Approved	[redacted] Date of signature: 02-Dec-2024 08:03:40 GMT+0000
Reason for signing: Approved	[redacted] Date of signature: 02-Dec-2024 08:20:39 GMT+0000

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