EU Clinical Trials Register

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

Summary

EudraCT number	2018-004530-14
Trial protocol	ES PT FI NO DK FR CZ PL GR HU GB DE BE IT
Global end of trial date	24 May 2022

Results information

Result version number	v3 (current)
This version publication date	16 April 2023
First version publication date	15 December 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1199-0337

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001006-PIP05-18
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2022
Global end of trial reached?	Yes
Global end of trial date	24 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Treatment interruption and dose reduction were allowed as medically indicated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Mexico: 2

Worldwide total number of subjects	39
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	12
Adolescents (12-17 years)	27
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter, multinational clinical trial in children and adolescents (6 to 17 years old) with clinically significant fibrosing Interstitial Lung Disease (ILD) in two parts. A randomised, placebo-controlled, double-blind period (DBP) of 24 weeks was followed by an open-label Nintedanib period (OLNP) of variable duration.

Pre-assignment

Screening details:

Only subjects that met all inclusion and none exclusion criteria could enter the study. Subjects were free to withdraw at any time for any reason given. Subjects were monitored throughout the trial conduct. Treatment interruption and dose reduction were allowed as medically indicated.

Period 1

Period 1 title	Double-blind period (DBP)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

Subjects, investigators and any other site personnel remained blinded with regard to the randomised treatment assignments until after the final database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	DBP+OLNP: Randomised to placebo

Arm description:

This arm shows placebo randomised subjects treated orally with a Nintedanib matching placebo soft capsule twice daily (DBP).
Subjects who continued with the open-label Nintedanib period (OLNP) after the DBP switched to active Nintedanib treatment and were treated orally with Nintedanib twice daily (OLNP).

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dosing interval was approximately 12 hours from one dose to the next dose in the DBP and OLNP.

In this arm subjects received placebo first (DBP), then Nintedanib (OLNP).
DBP: Planned was from 1st randomised trial to last blinded drug intake. OLNP: Planned was from 1st open-label to last open-label Nintedanib intake.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dose interval was approximately 12 hours from one to the next dose.

Arm title	DBP+OLNP: Randomised to Nintedanib

Arm description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib in the DBP and OLNP twice daily.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dosing interval was approximately 12 hours from one dose to the next dose in the DBP and OLNP.

In this arm subjects received Nintedanib only (DBP+OLNP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.
DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dose interval was approximately 12 hours from one to the next dose.

Number of subjects in period 1	DBP+OLNP: Randomised to placebo	DBP+OLNP: Randomised to Nintedanib
Started	13	26
Completed	11	21
Not completed	2	5
Discontinued treatment due to adverse event	-	2
Completed prematurely due to administrative EoT	2	2
Discontinued treatment due to other reason	-	1

Period 2

Period 2 title	Open-label Nintedanib period (OLNP)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding in the OLNP

Arms

Are arms mutually exclusive?	Yes

Arm title	DBP+OLNP: Randomised to placebo

Arm description:

This arm shows placebo randomised subjects treated orally with a Nintedanib matching placebo soft capsule twice daily (DBP).
Subjects who continued with the open-label Nintedanib period (OLNP) after the DBP switched to active Nintedanib treatment and were treated orally with Nintedanib twice daily (OLNP).

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dosing interval was approximately 12 hours from one dose to the next dose in the DBP and OLNP.

In this arm subjects received placebo first (DBP), then Nintedanib (OLNP).
DBP: Planned was from 1st randomised trial to last blinded drug intake. OLNP: Planned was from 1st open-label to last open-label Nintedanib intake.

Arm type	Placebo
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Medication dosage was per administration 50 milligram (mg) [2 capsules with strength 25 mg],75 mg [3 capsules with strength 25 mg], 100 mg [1 capsule with strength 100 mg or 4 capsules with strength 25 mg] or 150 mg [1 capsule with strength 150 mg or 6 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dose interval was approximately 12 hours from one to the next dose.

Arm title	DBP+OLNP: Randomised to Nintedanib

Arm description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib in the DBP and OLNP twice daily.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dosing interval was approximately 12 hours from one dose to the next dose in the DBP and OLNP.

In this arm subjects received Nintedanib only (DBP+OLNP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.
DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Medication dosage was per administration 50 milligram (mg) [2 capsules with strength 25 mg],75 mg [3 capsules with strength 25 mg], 100 mg [1 capsule with strength 100 mg or 4 capsules with strength 25 mg] or 150 mg [1 capsule with strength 150 mg or 6 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dose interval was approximately 12 hours from one to the next dose.

Number of subjects in period 2	DBP+OLNP: Randomised to placebo	DBP+OLNP: Randomised to Nintedanib
Started	11	21
Completed	11	20
Not completed	0	1
Discontinuation of trial medication - other reason	-	1

Baseline characteristics

Reporting groups

Reporting group title	DBP+OLNP: Randomised to placebo

Reporting group description:

This arm shows placebo randomised subjects treated orally with a Nintedanib matching placebo soft capsule twice daily (DBP).
Subjects who continued with the open-label Nintedanib period (OLNP) after the DBP switched to active Nintedanib treatment and were treated orally with Nintedanib twice daily (OLNP).

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dosing interval was approximately 12 hours from one dose to the next dose in the DBP and OLNP.

In this arm subjects received placebo first (DBP), then Nintedanib (OLNP).
DBP: Planned was from 1st randomised trial to last blinded drug intake. OLNP: Planned was from 1st open-label to last open-label Nintedanib intake.

Reporting group title	DBP+OLNP: Randomised to Nintedanib

Reporting group description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib in the DBP and OLNP twice daily.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dosing interval was approximately 12 hours from one dose to the next dose in the DBP and OLNP.

In this arm subjects received Nintedanib only (DBP+OLNP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.
DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Reporting group values	DBP+OLNP: Randomised to placebo	DBP+OLNP: Randomised to Nintedanib	Total
Number of subjects	13	26	39
Age categorical			
Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	4	8	12
Adolescents (12-17 years)	9	18	27
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.			
Units: years			

arithmetic mean	12.9	12.5	
standard deviation	± 2.8	± 3.6	-

Sex: Female, Male			
Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.			
Units: Subjects			
Female	5	10	15
Male	8	16	24

Race (NIH/OMB)			
Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	0	2	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	3	3
White	12	19	31
More than one race	0	0	0
Unknown or Not Reported	0	1	1

Ethnicity (NIH/OMB)			
Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.			
Units: Subjects			
Hispanic or Latino	5	7	12
Not Hispanic or Latino	8	18	26
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	DBP+OLNP: Randomised to placebo

Reporting group description:

This arm shows placebo randomised subjects treated orally with a Nintedanib matching placebo soft capsule twice daily (DBP).
Subjects who continued with the open-label Nintedanib period (OLNP) after the DBP switched to active Nintedanib treatment and were treated orally with Nintedanib twice daily (OLNP).

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dosing interval was approximately 12 hours from one dose to the next dose in the DBP and OLNP.

In this arm subjects received placebo first (DBP), then Nintedanib (OLNP).
DBP: Planned was from 1st randomised trial to last blinded drug intake. OLNP: Planned was from 1st open-label to last open-label Nintedanib intake.

Reporting group title	DBP+OLNP: Randomised to Nintedanib

Reporting group description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib in the DBP and OLNP twice daily.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. The dosing interval was approximately 12 hours from one dose to the next dose in the DBP and OLNP.

In this arm subjects received Nintedanib only (DBP+OLNP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.
DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

from first open-label Nintedanib intake to last open-label Nintedanib intake.

Subject analysis set title	DBP+OLNP: 6 to < 12 years - exposed to Nintedanib
Subject analysis set type	Per protocol

Subject analysis set description:

This arm shows subjects aged 6 to < 12 years old who were exposed to Nintedanib only, either randomised placebo (treated with Nintedanib in the OLNP only) and randomised Nintedanib (treated with Nintedanib in both, DBP and OLNP).The 6 to < 12 years old subjects were treated orally with Nintedanib twice daily with a dose interval of approximately 12 hours from one dose to the next dose.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received Nintedanib only (OLNP or DBP+OLNP).
DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Subject analysis set title	DBP+OLNP: 12 to < 18 years - exposed to Nintedanib
Subject analysis set type	Per protocol

Subject analysis set description:

This arm shows subjects aged 12 to <18 years old who were exposed to Nintedanib only either randomised placebo (treated with Nintedanib in the OLNP only) and randomised Nintedanib (treated with Nintedanib in both, DBP and OLNP). The 12 to 18 years old subjects were treated orally with Nintedanib twice daily with a dose interval of approximately 12 hours from one dose to the next dose.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received Nintedanib only (OLNP or DBP+OLNP). DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Subject analysis set title	DBP: Randomised to placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows placebo randomised subjects treated orally with a Nintedanib matching placebo soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received placebo only (DBP).
DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to Nintedanib
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib in the DBP twice daily with a dose interval of approximately 12 hours from one dose to the next dose.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received Nintedanib only (DBP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.
DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	OLNP: Randomised to placebo and switched to Nintedanib
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows subjects who continued with the open-label Nintedanib period (OLNP) after the DBP, switched to active Nintedanib treatment in the OLNP and were treated orally with Nintedanib twice daily with a dose interval of approximately 12 hours from one dose to the next dose.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received placebo first (DBP) and then Nintedanib (OLNP). DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Subject analysis set title	DBP+OLNP: Randomised to placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows subjects who continued with the open-label Nintedanib period (OLNP) after the DBP, switched to active Nintedanib treatment in the OLNP and were treated orally with Nintedanib twice daily with a dose interval of approximately 12 hours from one dose to the next dose.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received placebo first (DBP) and then Nintedanib (OLNP). DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Subject analysis set title	DBP + OLNP: Randomised to Nintedanib
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib in the DBP and OLNP twice daily with a dose interval of approximately 12 hours from one dose to the next dose.

Medication dosage was per administration 50 milligram (mg) [2x25 mg capsules (cap)],75 mg [3x25 mg cap], 100 mg [1x100 mg cap or 4x25 mg cap] or 150 mg [1x150 mg cap or 6x25 mg cap] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received Nintedanib in both periods (DBP + OLNP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.
DBP: Planned was from first randomised trial drug intake to last blinded drug intake.
OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Subject analysis set title	DBP: Randomised to placebo - capsule size of 25 mg capsule
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows placebo randomised subjects treated orally with placebo soft capsules of 25 milligram (mg) with a capsule size of 5 millimeter (mm) diameter and 8 mm length, oval shaped, twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage per administration was 50 milligram (mg) [2 capsules with strength 25 mg], 75 mg [3 capsules with strength 25 mg], 100 mg [4 capsules with strength 25 mg] or 150 mg [6 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received placebo only (DBP).

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to Nintedanib - capsule size of 25 mg capsule
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib soft capsules of 25 milligram (mg) with a capsule size of 5 millimeter (mm) diameter and 8 mm length, oval shaped, twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind

period (DBP).

Medication dosage per administration was 50 milligram (mg) [2 capsules with strength 25 mg], 75 mg [3 capsules with strength 25 mg], 100 mg [4 capsules with strength 25 mg] or 150 mg [6 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received Nintedanib only (DBP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to placebo - capsule size of 100 mg capsule
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows placebo randomised subjects treated orally with placebo soft capsules of 100 mg with a capsule size of 6 mm diameter and 16 mm length, oblong shaped, twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage per administration was 100 mg [1 capsules with strength 100 mg] based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received placebo only (DBP).

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to Nintedanib - capsule size of 100 mg capsule
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib soft capsules of 100 mg with a capsule size of 6 mm diameter and 16 mm length, oblong shaped, twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage per administration was 100 mg [1 capsules with strength 100 mg] based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received Nintedanib only (DBP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to placebo - capsule size of 150 mg capsule
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows placebo randomised subject treated orally with placebo soft capsules of 150 mg with a capsule size of 7 mm diameter and 18 mm length, oblong shaped, twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage per administration was 150 mg [1 capsules with strength 150 mg] based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received placebo only (DBP).

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to Nintedanib - capsule size of 150 mg capsule
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib soft capsules of 150 mg with a capsule size of 7 mm diameter and 18 mm length, oblong shaped, twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage per administration was 150 mg [1 capsules with strength 150 mg] based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received Nintedanib only (DBP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to placebo - 2 capsules
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows placebo randomised subjects treated orally with 1 Nintedanib matching placebo soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage was per administration 100 mg [1 capsule with strength 100 mg] or 150 mg [1 capsule with strength 150 mg] based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received placebo only (DBP).

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to Nintedanib - 2 capsules
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows Nintedanib randomised subjects treated orally with 1 Nintedanib soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage was per administration 100 mg [1 capsule with strength 100 mg] or 150 mg [1 capsule with strength 150 mg] based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received Nintedanib only (DBP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to placebo - 4 capsules
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows placebo randomised subjects treated orally with 2 Nintedanib matching placebo soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage was per administration 50 milligram (mg) [2 capsules with strength 25 mg], based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received placebo only (DBP).

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to Nintedanib - 4 capsules
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows Nintedanib randomised subjects treated orally with 2 Nintedanib soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage was per administration 50 milligram (mg) [2 capsules with strength 25 mg], based on the subject's weight at baseline (= 0 weeks).

In this arm subjects received Nintedanib only (DBP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to placebo - 6 capsules
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows placebo randomised subjects treated orally with 3 Nintedanib matching placebo soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage was per administration 75 mg [3 capsules with strength 25 mg] based on the

subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received placebo only (DBP).

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to Nintedanib - 6 capsules
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows Nintedanib randomised subjects treated orally with 3 Nintedanib soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage was per administration 75 mg [3 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received Nintedanib only (DBP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arm.

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Subject analysis set title	DBP: Randomised to placebo - >6 capsules
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This arm shows placebo randomised subjects treated orally with >3 Nintedanib matching placebo soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP).

Medication dosage was per administration 100 mg [4 capsules with strength 25 mg] or 150 mg [6 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed.

In this arm subjects received placebo only (DBP).

DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Primary: Area under the plasma concentration-time curve at steady state (AUCτ,ss) based on sampling at steady state (at Week 2 and Week 26)

End point title	Area under the plasma concentration-time curve at steady state (AUCτ,ss) based on sampling at steady state (at Week 2 and Week 26)[1]

End point description:

Area under the plasma concentration-time curve at steady state (AUCt,ss) based on sampling at steady state (at Week 2 and Week 26) after multiple oraladministration of Nintedanib by age group over all treatments.

Values of samples taken at Week 2 (for randomised Nintedanib subjects) and at Week 26 (for randomised placebo subjects) were used. Missing values at Week 2 of randomised Nintedanib subjects were replaced with values taken at Week 26.

Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one pharmacokinetic (PK) endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability.

End point type	Primary

End point timeframe:

At Week 2 and at Week 26: at 5 minutes before and at 0, 1, 2, 3, 4, 6, and 8 hours post administration of the morning dose

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	DBP+OLNP: 6 to < 12 years - exposed to Nintedanib	DBP+OLNP: 12 to < 18 years - exposed to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	23		
Units: Hours timesnanogram per milliliter				
geometric mean (geometric coefficient of variation)	175 (± 85.1)	167 (± 83.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment-emergent adverse events during the double-blind period

End point title	Number of subjects with treatment-emergent adverse events during the double-blind period[2]

End point description:

Treatment-emergent was defined as: Adverse events with onset or worsening on or after date of treatment start until end of double-blind period (defined as the day before first intake of open-label nintedanib or last double-blind drug intake + residual effect period, whichever is earlier) were considered as treatment-emergent and were included in the analysis. Adverse events were counted under the treatment as randomized for the double-blind period.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Primary

End point timeframe:

From first drug administration until the earlier of (i) first intake of open−label nintedanib (exclusive) and (ii) last drug intake, up to 28 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	26		
Units: Subjects	11	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with at least one treatment-emergent pathological finding of epiphyseal growth plate on imaging up to week 24, and week 52

End point title	Number of subjects with at least one treatment-emergent pathological finding of epiphyseal growth plate on imaging up to week 24, and week 52

End point description:

Number of subjects with at least one treatment-emergent pathological finding of the epiphyseal growth plate imaging (Magnetic Resonance Imaging (MRI)s/x-rays) were analyzed cumulatively and based on central review.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to Week 24 (included values at Week 12 and Week 24); Up to Week 52 (included values at Week 12, 24, 36 and 52)

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	26		
Units: Subjects				
At Week 24	1	2		
At Week 52	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent pathological findings on dental examination or imaging up to week 24

End point title	Number of subjects with treatment-emergent pathological findings on dental examination or imaging up to week 24

End point description:

Number of subjects with treatment-emergent pathological findings on dental examination (clinical examination) based on dentist assessment or imaging (panoramic x-ray) based on central review were analyzed. Number of subjects with treatment-emergent pathological findings on dental imaging were analyzed cumulatively.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Dental examination: at Week 12 and Week 24; Dental imaging: at Week 24

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	26		
Units: Subjects				
Dental examination: Pathological findings	1	5		

Dental imaging: Stunted growth of dental root	0	6		
Dental imaging: Accelerated growth of dental root	0	0		
Dental imaging: extra / supernumerary teeth	0	0		
Dental imaging: Impacted permanent teeth	2	4		
Dental imaging: Additional findings	1	5		
Dental imaging: Other findings	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with at least one treatment-emergent pathological findings on dental examination or imaging up to week 52

End point title	Number of subjects with at least one treatment-emergent pathological findings on dental examination or imaging up to week 52

End point description:

Number of subjects with treatment-emergent pathological findings on dental examination (clinical examination) based on dentist assessment or imaging (panoramic x-ray) based on central review were analyzed. Number of subjects with treatment-emergent pathological findings on dental imaging were analyzed cumulatively.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Dental examination: at Week 12, 24, 36, and Week 52; Dental imaging: at Week 24 and at Week 52.

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	26		
Units: Subjects				
Dental examination: Pathological findings	3	7		
Dental imaging: Stunted growth of dental root	0	6		
Dental imaging: Accelerated growth of dental root	0	0		
Dental imaging: extra / supernumerary teeth	0	0		
Dental imaging: Impacted permanent teeth	2	5		
Dental imaging: Additional findings	1	6		
Dental imaging: Other findings	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in height at Week 24

End point title	Absolute change from baseline in height at Week 24

End point description:

Absolute change from baseline in height at Week 24 was measured with a stadiometer 3 times at each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in height at Week 24 in the treated set (TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements pre-administration at -4 weeks and at 0, 12, 24, 36, 52, 64, 76, and 88 weeks after first drug administration. MMRM values at Week 24 are reported in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	25		
Units: Centimeter				
least squares mean (confidence interval 95%)	1.3 (0.6 to 1.9)	1.3 (0.8 to 1.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

No formal hypotheses were tested

Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9858
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Number of subjects with treatment-emergent adverse events over the whole trial

End point title	Number of subjects with treatment-emergent adverse events over the whole trial

End point description:

Treatment-emergent was defined as: Adverse events with onset or worsening on or after date of treatment start until last drug intake + residual effect period was considered as treatment-emergent and was included in the analysis. Adverse events were counted under the treatment as randomized for the double-blind period.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Secondary

End point timeframe:

From first drug administration until the last drug intake, up to 92 weeks

End point values	DBP: Randomised to placebo	OLNP: Randomised to placebo and switched to Nintedanib	DBP + OLNP: Randomised to Nintedanib	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	11	26	
Units: Subjects	11	11	26	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in height at Week 52

End point title	Absolute change from baseline in height at Week 52

End point description:

Absolute change from baseline in height at Week 52 was measured with a stadiometer 3 times at each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in height at Week 52 in the treated set (TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subjects. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements pre-administration at -4 weeks and at 0, 12, 24, 36, 52, 64, 76, and 88 weeks after first drug administration. MMRM values at Week 52 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	25		
Units: Centimeter				
least squares mean (confidence interval 95%)	2.8 (1.5 to 4.2)	2.8 (1.8 to 3.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

No formal hypotheses were tested

Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9769
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.8

Secondary: Absolute change from baseline in height at Week 76

End point title	Absolute change from baseline in height at Week 76

End point description:

Absolute change from baseline in height at Week 76 was measured with a stadiometer 3 times at each time point. The average of these 3 measurements was taken per time point.

MMRM has been calculated but did not provide estimates for this time point due to low sample size. Thus, change in height from baseline to Week 76 was analyzed descriptively only.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

Measurements were assessed at Week 0 and at Week 76

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	4		
Units: Centimeter				
arithmetic mean (standard deviation)				
At Baseline	143.7 (± 11.2)	162.5 (± 15.8)		
At Week 76	150.0 (± 15.7)	165.5 (± 13.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in sitting height at Week 24

End point title	Absolute change from baseline in sitting height at Week 24

End point description:

Absolute change from baseline in sitting height at Week 24 was measured with a stadiometer 3 times at each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in sitting height at Week 24 in the treated set (TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements pre-administration at -4 weeks and at 0, 12, 24, 36, 52, 64, 76, and 88 weeks after first drug administration. MMRM values at Week 24 are reported in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	15		
Units: Centimeters				
least squares mean (confidence interval 95%)	1.0 (-1.3 to 3.4)	2.1 (0.6 to 3.6)		

Statistical analyses

Statistical analysis title	Statistical analysis 3
Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4442
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	4
Variability estimate	Standard error of the mean
Dispersion value	1.4

Secondary: Absolute change from baseline in sitting height at Week 52

End point title	Absolute change from baseline in sitting height at Week 52

End point description:

Absolute change from baseline in sitting height at Week 52 was measured with a stadiometer 3 times at each time point. The average of these 3 measurements was taken per time point.

MMRM has been calculated but did not provide estimates for this time point due to low sample size. Thus, change in sitting height from baseline to Week 52 was analyzed descriptively only.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication. Only subjects with non-missing results were included in the analysis.

End point type	Secondary

End point timeframe:

Measurements were assessed at Week 0 and at Week 52

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	7		
Units: Centimeters				
arithmetic mean (standard deviation)				
At Baseline	78.7 (± 11.8)	77.6 (± 9.4)		
At Week 52	79.0 (± 12.2)	79.3 (± 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in sitting height at Week 76

End point title	Absolute change from baseline in sitting height at Week 76

End point description:

Absolute change from baseline in sitting height at Week 76 was measured with a stadiometer 3 times at each time point. The average of these 3 measurements was take per time point.

MMRM has been calculated but did not provide estimates for this time point due to low sample size. Thus, change in sitting height from baseline to Week 76 was analyzed descriptively only.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication. Only subjects with non-missing results were included in the analysis.

99999= Not calculable

End point type	Secondary

End point timeframe:

Measurements were assessed at Week 0 and at Week 76

End point values	DBP+OLNP: Randomised to placebo	DBP+OLNP: Randomised to Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: Centimeters				
arithmetic mean (standard deviation)				
At Baseline	65.0 (± 99999)	83.0 (± 4.2)		
At Week 76	65.0 (± 99999)	84.5 (± 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in leg length at Week 24 - left

End point title	Absolute change from baseline in leg length at Week 24 - left

End point description:

Absolute change from baseline in left leg length at Week 24 was assessed by measuring distance between anterior iliac spine and medial malleolus 3 times at each leg and each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in left leg length at Week 24 in the treated set (TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 12, 24, 36, 52, 64, and 76 weeks after first drug administration. MMRM values at Week 24 are reported in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	23		
Units: Centimeters				
least squares mean (confidence interval 95%)	1.6 (0.3 to 2.9)	1.7 (0.8 to 2.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 4
Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.882
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.8

Secondary: Absolute change from baseline in leg length at Week 52 - left

End point title	Absolute change from baseline in leg length at Week 52 - left

End point description:

Absolute change from baseline in left leg length at Week 52 was assessed by measuring distance between anterior iliac spine and medial malleolus 3 times at each leg and each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in left leg length at Week 52 in the treated set (TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 12, 24, 36, 52, 64, and 76 weeks after first drug administration. MMRM values at Week 52 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	23		
Units: Centimeter				
least squares mean (confidence interval 95%)	2.8 (0.3 to 5.4)	2.9 (0.9 to 4.9)		

Statistical analyses

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
No formal hypotheses were tested	
Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9652
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	1.6

Secondary: Absolute change from baseline in leg length at Week 76 - left

End point title	Absolute change from baseline in leg length at Week 76 - left

End point description:

Absolute change from baseline in left leg length at Week 76 was assessed by measuring distance between anterior iliac spine and medial malleolus 3 times at each leg and each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in left leg length at Week 76 was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 12, 24, 36, 52, 64, and 76 weeks after first drug administration. MMRM values at Week 76 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	23		
Units: Centimeter				
least squares mean (confidence interval 95%)	5.2 (-0.0 to 10.5)	2.6 (−1.5 to 6.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 6
Statistical analysis description:	
No formal hypotheses were tested	
Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4084
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	4
Variability estimate	Standard error of the mean
Dispersion value	3.1

Secondary: Absolute change from baseline in leg length at Week 24 - right

End point title	Absolute change from baseline in leg length at Week 24 - right

End point description:

Absolute change from baseline in right leg length at Week 24 was assessed by measuring distance between anterior iliac spine and medial malleolus 3 times at each leg and each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in right leg length at Week 24 in the treated set (TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 12, 24, 36, 52, 64, and 76 weeks after first drug administration. MMRM values at Week 24 are reported in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	23		
Units: Centimeters				
least squares mean (confidence interval 95%)	1.6 (0.3 to 2.9)	1.6 (0.6 to 2.6)		

Statistical analyses

Statistical analysis title	Statistical analysis 7
Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9928
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.8

Secondary: Absolute change from baseline in leg length at Week 52 - right

End point title	Absolute change from baseline in leg length at Week 52 - right

End point description:

Absolute change from baseline in right leg length at Week 52 was assessed by measuring distance between anterior iliac spine and medial malleolus 3 times at each leg and each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in right leg length at Week 52 in the treated set (TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 12, 24, 36, 52, 64, and 76 weeks after first drug administration. MMRM values at Week 52 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	23		
Units: Centimeter				
least squares mean (confidence interval 95%)	2.8 (0.4 to 5.1)	3.4 (1.6 to 5.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 8
Statistical analysis description:	
No formal hypotheses were tested	
Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6366
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	3.6
Variability estimate	Standard error of the mean
Dispersion value	1.4

Secondary: Absolute change from baseline in leg length at Week 76 - right

End point title	Absolute change from baseline in leg length at Week 76 - right

End point description:

Absolute change from baseline in right leg length at Week 76 was assessed by measuring distance between anterior iliac spine and medial malleolus 3 times at each leg and each time point. The average of these 3 measurements was taken per time point.

Absolute change from baseline in right leg length was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 12, 24, 36, 52, 64, and 76 weeks after first drug administration. MMRM values at Week 76 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	23		
Units: Centimeter				
least squares mean (confidence interval 95%)	3.9 (-0.5 to 8.3)	4.3 (0.8 to 7.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 9
Statistical analysis description:	
No formal hypotheses were tested	
Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8823
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	5.9
Variability estimate	Standard error of the mean
Dispersion value	2.3

Secondary: Absolute change from baseline in Forced Vital Capacity (FVC) % predicted at Week 24

End point title	Absolute change from baseline in Forced Vital Capacity (FVC) % predicted at Week 24

End point description:

Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. The predicted values were calculated according to the Global Lungs Initiative (GLI) 2012 equations.

Absolute change from baseline in FVC % predicted was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements pre-administration at -4 weeks and at 0, 2, 6, 12, 24, 26, 36, and 52 weeks after first drug administration. MMRM values at Week 24 are reported in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	26		
Units: Percentage of predicted FVC				
least squares mean (confidence interval 95%)	-0.8939 (-4.6090 to 2.8211)	0.3112 (-2.3595 to 2.9820)		

Statistical analyses

Statistical analysis title	Statistical analysis 10
Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5962
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	1.2052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3966
upper limit	5.807
Variability estimate	Standard error of the mean
Dispersion value	2.2491

Secondary: Absolute change from baseline in Forced Vital Capacity (FVC) % predicted at Week 52

End point title	Absolute change from baseline in Forced Vital Capacity (FVC) % predicted at Week 52

End point description:

Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. The predicted values were calculated according to the Global Lungs Initiative (GLI) 2012 equations.

Absolute change from baseline in FVC % predicted was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements pre-administration at -4 weeks and at 0, 2, 6, 12, 24, 26, 36, and 52 weeks after first drug administration. MMRM values at Week 52 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	26		
Units: Percentage of predicted FVC				
least squares mean (confidence interval 95%)	-0.9827 (-6.2611 to 4.2958)	0.7906 (-2.9464 to 4.5277)		

Statistical analyses

Statistical analysis title	Statistical analysis 11
Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5776
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	1.7733
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7015
upper limit	8.2481
Variability estimate	Standard error of the mean
Dispersion value	3.1424

Secondary: Absolute change from baseline in Pediatric Quality of Life Questionnaire™(PedsQL™) at Week 24 - parent report

End point title	Absolute change from baseline in Pediatric Quality of Life Questionnaire™(PedsQL™) at Week 24 - parent report

End point description:

The PedsQL™ questionnaires is based on 23 items, 5-point Likert scale (0 = never (worst outcome) to 4=almost always (best outcome)). Items were reverse-scored and linearly transformed to a 0-100 scale (0 = 100 to 4 = 0). Higher scores indicated better health-related quality of life. To create total scores, the mean was computed.

Absolute change from baseline was based on a MMRM, with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 24, and 52 weeks after first drug administration. MMRM values at Week 24 are reported
in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	21		
Units: Unit on scale				
least squares mean (confidence interval 95%)	5.615 (-1.506 to 12.736)	5.481 (0.384 to 10.578)		

Statistical analyses

Statistical analysis title	Statistical analysis 12
Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9755
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.134
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.975
upper limit	8.707
Variability estimate	Standard error of the mean
Dispersion value	4.316

Secondary: Absolute change from baseline in Pediatric Quality of Life Questionnaire™(PedsQL™) at Week 52 - parent report

End point title	Absolute change from baseline in Pediatric Quality of Life Questionnaire™(PedsQL™) at Week 52 - parent report

End point description:

The PedsQL™ questionnaires is based on 23 items, 5-point Likert scale (0 = never (worst outcome) to 4=almost always (best outcome)). Items were reverse-scored and linearly transformed to a 0-100 scale (0 = 100 to 4 = 0). Higher scores indicated better health-related quality of life. To create total scores, the mean was computed.

Absolute change from baseline was based on a MMRM, with fixed categorical effects of (randomised)

treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary
End point timeframe:	

MMRM included measurements at 0, 24, and 52 weeks after first drug administration. MMRM values at Week 52 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	21		
Units: Unit on scale				
least squares mean (confidence interval 95%)	4.377 (-4.403 to 13.157)	7.830 (1.799 to 13.862)		

Statistical analyses

Statistical analysis title	Statistical analysis 13
Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.514
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	3.453
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.25
upper limit	14.157
Variability estimate	Standard error of the mean
Dispersion value	5.225

Secondary: Absolute change from baseline in Pediatric Quality of Life Questionnaire™(PedsQL™) at Week 24 - subject report

End point title	Absolute change from baseline in Pediatric Quality of Life Questionnaire™(PedsQL™) at Week 24 - subject report
End point description:	

The PedsQL™ questionnaires is based on 23 items, 5-point Likert scale (0 = never (worst outcome) to 4=almost always (best outcome)). Items were reverse-scored and linearly transformed to a 0-100 scale

(0 = 100 to 4 = 0). Higher scores indicated better health-related quality of life. To create total scores, the mean was computed.

Absolute change from baseline was based on a MMRM, with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 24, and 52 weeks after first drug administration. MMRM values at Week 24 are reported in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	21		
Units: Unit on scale				
least squares mean (confidence interval 95%)	5.484 (-0.051 to 11.018)	6.514 (2.531 to 10.497)		

Statistical analyses

Statistical analysis title	Statistical analysis 14
Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7613
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.848
upper limit	7.908
Variability estimate	Standard error of the mean
Dispersion value	3.358

Secondary: Absolute change from baseline in Pediatric Quality of Life Questionnaire™(PedsQL™) at Week 52 - subject report

End point title	Absolute change from baseline in Pediatric Quality of Life Questionnaire™(PedsQL™) at Week 52 - subject report

End point description:

The PedsQL™ questionnaires is based on 23 items, 5-point Likert scale (0 = never (worst outcome) to 4=almost always (best outcome)). Items were reverse-scored and linearly transformed to a 0-100 scale (0 = 100 to 4 = 0). Higher scores indicated better health-related quality of life. To create total scores, the mean was computed.

Absolute change from baseline was based on a MMRM, with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 24, and 52 weeks after first drug administration. MMRM values at Week 52 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	21		
Units: Unit on scale				
least squares mean (confidence interval 95%)	0.902 (-7.616 to 9.420)	1.243 (-4.598 to 7.083)		

Statistical analyses

Statistical analysis title	Statistical analysis 15
Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9468
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.026
upper limit	10.707
Variability estimate	Standard error of the mean
Dispersion value	5.049

Secondary: Absolute change from baseline in oxygen saturation (SpO) on room air

at rest at Week 24

End point title	Absolute change from baseline in oxygen saturation (SpO) on room air at rest at Week 24

End point description:

Oxygen saturation (SpO) was measured after minimum 5 minutes on room air by standard pulse oximetry at rest.

Absolute change from baseline in SpO at Week 24 in the treated set (TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements pre-administration at -4 weeks and at 0, 2, 6, 12, 24, 26, 36, and 52 weeks after first drug administration. MMRM values at Week 24 are reported in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	26		
Units: Percentage of SpO				
least squares mean (confidence interval 95%)	-2.25 (-4.45 to -0.04)	0.07 (-1.49 to 1.63)		

Statistical analyses

Statistical analysis title	Statistical analysis 16
Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0908
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	5.02
Variability estimate	Standard error of the mean
Dispersion value	1.33

Secondary: Absolute change from baseline in oxygen saturation (SpO) on room air at rest at Week 52

End point title	Absolute change from baseline in oxygen saturation (SpO) on room air at rest at Week 52

End point description:

Oxygen saturation (SpO) was measured after minimum 5 minutes on room air by standard pulse oximetry at rest.
Absolute change from baseline in SpO at Week 52 in the treated set(TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements pre-administration at -4 weeks and at 0, 2, 6, 12, 24, 26, 36, and 52 weeks after first drug administration. MMRM values at Week 52 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP+OLNP: Randomised to Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: Percentage of SpO				
least squares mean (confidence interval 95%)	-2.60 (-5.02 to -0.18)	-0.32 (-2.03 to 1.40)		

Statistical analyses

Statistical analysis title	Statistical analysis 17
Comparison groups	DBP+OLNP: Randomised to Nintedanib v DBP+OLNP: Randomised to placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1222
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	5.25

Variability estimate	Standard error of the mean
Dispersion value	1.39

Secondary: Absolute change from baseline in 6 minutes (min) walk distance at Week 24

End point title	Absolute change from baseline in 6 minutes (min) walk distance at Week 24

End point description:

Absolute change from baseline in 6 minutes (min) walk distance at Week 24 in the treated set(TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 24, and 52 weeks after first drug administration. MMRM values at Week 24 are reported in the table below

End point values	DBP: Randomised to placebo	DBP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	21		
Units: Meter				
least squares mean (confidence interval 95%)	10.5 (-36.4 to 57.3)	17.6 (-16.2 to 51.5)		

Statistical analyses

Statistical analysis title	Statistical analysis 18
Comparison groups	DBP: Randomised to placebo v DBP: Randomised to Nintedanib
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8012
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.7
upper limit	65

Variability estimate	Standard error of the mean
Dispersion value	28.2

Secondary: Subjects acceptability based on the size of capsules at Week 24 - patient question

End point title	Subjects acceptability based on the size of capsules at Week 24 - patient question

End point description:

Acceptability is the overall ability and willingness of subjects to use medicinal products as intended. Acceptability based on capsule size was assessed by an acceptability questionnaire (1 item and 3 categories) for subjects. In case the subject was considered not old enough as per investigator judgment the caregiver could assist with completion. Additionally to the commercially available 100 milligram (mg) soft capsules (oblong shape, 6 millimeter (mm) diameter, 16 mm length) and 150 mg soft capsules (oblong shape, 7 mm diameter, 18 mm length), 25 mg Nintedanib soft capsules of smaller size (oval shape, 5 mm diameter, 8 mm length) were provided for subjects who were assigned to a dose smaller than 100 mg or were unable to swallow the larger 100 mg or 150 mg capsules.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication. Only subjects with non-missing results were included in the analysis.

End point type	Secondary

End point timeframe:

Acceptability was assessed at Week 24

End point values	DBP: Randomised to placebo - capsule size of 25 mg capsule	DBP: Randomised to Nintedanib - capsule size of 25 mg capsule	DBP: Randomised to placebo - capsule size of 100 mg capsule	DBP: Randomised to Nintedanib - capsule size of 100 mg capsule
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	6	4	14
Units: Subjects				
OK	4	6	4	14
Large	0	0	0	0
Very Large	0	0	0	0

End point values	DBP: Randomised to placebo - capsule size of 150 mg capsule	DBP: Randomised to Nintedanib - capsule size of 150 mg capsule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	2		
Units: Subjects				
OK	3	2		
Large	0	0		
Very Large	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in 6 minutes (min) walk distance at Week 52

End point title	Absolute change from baseline in 6 minutes (min) walk distance at Week 52

End point description:

Absolute change from baseline in 6 minutes (min) walk distance at Week 52 in the treated set(TS) was based on a Mixed Model Repeated Measures (MMRM), with fixed categorical effects of (randomised) treatment at each visit, age−group and the fixed continuous effects of baseline at each visit, and random effect for subject. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within−subject measurements.

Treated set (TS): The TS consisted of participants who were randomised to a treatment group and received at least one dose of study medication. Only participants with correctly measured baseline and at least one post-baseline measurement were included in the analysis.

End point type	Secondary

End point timeframe:

MMRM included measurements at 0, 24, and 52 weeks after first drug administration. MMRM values at Week 52 are reported in the table below

End point values	DBP+OLNP: Randomised to placebo	DBP + OLNP: Randomised to Nintedanib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	21		
Units: Meter (m)				
least squares mean (confidence interval 95%)	28.1 (-29.4 to 85.5)	-4.9 (-44.5 to 34.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 19
Comparison groups	DBP+OLNP: Randomised to placebo v DBP + OLNP: Randomised to Nintedanib
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3401
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Mean Difference
Point estimate	-32.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-103.1
upper limit	37.2
Variability estimate	Standard error of the mean
Dispersion value	33.8

Secondary: Subjects acceptability based on the size of capsules at Week 24 - investigator question

End point title	Subjects acceptability based on the size of capsules at Week 24 - investigator question

End point description:

Acceptability the overall ability and willingness of subjects to use medicinal products as intended. Acceptability based on the capsule size was assessed by an acceptability questionnaire (1 item with 3 categories) for investigators.

In addition to the commercially available 100 milligram (mg) soft capsules (oblong shape, 6 millimeter (mm) diameter, 16 mm length) and 150 mg soft capsules (oblong shape, 7 mm diameter, 18 mm length), 25 mg Nintedanib soft capsules of smaller size (oval shape, 5 mm diameter, 8 mm length) were provided in this trial for subjects who were assigned to a dose smaller than 100 mg or were unable to swallow the larger 100 mg or 150 mg capsules.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Acceptability was assessed at Week 24

End point values	DBP: Randomised to placebo - capsule size of 25 mg capsule	DBP: Randomised to Nintedanib - capsule size of 25 mg capsule	DBP: Randomised to placebo - capsule size of 100 mg capsule	DBP: Randomised to Nintedanib - capsule size of 100 mg capsule
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	6	4	14
Units: Subjects				
No	1	2	1	2
Yes	0	0	0	0
Missing	3	4	3	12

End point values	DBP: Randomised to placebo - capsule size of 150 mg capsule	DBP: Randomised to Nintedanib - capsule size of 150 mg capsule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	2		

Units: Subjects				
No	0	1		
Yes	0	0		
Missing	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects acceptability based on the number of capsules at Week 24 - patient question

End point title	Subjects acceptability based on the number of capsules at Week 24 - patient question

End point description:

Acceptability is the overall ability and willingness of subjects to use medicinal products as intended. Acceptability based on capsule number was assessed by an acceptability questionnaire (1 item with 3 categories). If subjects were not old enough the caregiver could assist. Additionally to the commercially available 100 milligram (mg) soft capsules ((SCa) oblong shape, 6 millimeter (mm) diameter, 16 mm length) and 150 mg SCa (oblong shape, 7 mm diameter, 18 mm length), 25 mg Nintedanib smaller sized SCa (oval shape, 5 mm diameter, 8 mm length) were provided for subjects who were assigned to doses smaller than 100 mg or were unable to swallow the larger 100 mg or 150 mg capsules. Dosage was based on subject's weight. Capsule number per administration ranged from 2 to >6 .
Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication. Only subjects with non-missing results were included in the analysis.

End point type	Secondary

End point timeframe:

Acceptability was assessed at Week 24

End point values	DBP: Randomised to placebo - 2 capsules	DBP: Randomised to Nintedanib - 2 capsules	DBP: Randomised to placebo - 4 capsules	DBP: Randomised to Nintedanib - 4 capsules
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	16	2	3
Units: Subjects				
I had no problem swallowing them	7	16	2	3
I swallowed them but it was difficult	0	0	0	0
I could not swallow them sometimes	0	0	0	0

End point values	DBP: Randomised to placebo - 6 capsules	DBP: Randomised to Nintedanib - 6 capsules	DBP: Randomised to placebo - >6 capsules	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	3	1	
Units: Subjects				
I had no problem swallowing them	1	3	1	
I swallowed them but it was difficult	0	0	0	

I could not swallow them sometimes	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with occurrence of first respiratory-related hospitalization over the whole trial

End point title	Number of subjects with occurrence of first respiratory-related hospitalization over the whole trial

End point description:

Number of subjects with occurrence of first respiratory-related hospitalization over the whole trial.

The number of subjects with first respiratory-related hospitalization is reported instead of a metric summarizing the time-to-event data with unit of time, as the numbers resulting from the Kaplan-Meier-analysis were even below the first quartile.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Secondary

End point timeframe:

From first drug administration until the last drug intake + 28 days Residual Effect Period (REP), up to 92.6 weeks

End point values	DBP+OLNP: Randomised to placebo	DBP+OLNP: Randomised to Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: Subjects	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with occurrence of first acute Interstitial Lung Disease (ILD) exacerbation or death over the whole trial

End point title	Number of subjects with occurrence of first acute Interstitial Lung Disease (ILD) exacerbation or death over the whole trial

End point description:

Number of subjects with occurrence of first acute Interstitial Lung Disease (ILD) exacerbation or death over the whole trial. The number of subjects with first acute ILD exacerbation is reported instead of a metric summarizing the time-to-event data with unit of time, as the numbers resulting from the Kaplan-Meier-analysis were even below the first quartile.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Secondary

End point timeframe:

From first drug administration until the last drug intake + 28 days REP, up to 92.6 weeks

End point values	DBP+OLNP: Randomised to placebo	DBP+OLNP: Randomised to Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: Subjects	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with occurrence of death over the whole trial

End point title	Number of subjects with occurrence of death over the whole trial

End point description:

Number of subjects with occurrence of death over the whole trial over the whole trial was computed. The number of subjects with occurrence of death is reported instead of a metric summarizing the time-to-event data with unit of time, as the numbers resulting from the Kaplan-Meier-analysis were even below the first quartile.

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

End point type	Secondary

End point timeframe:

From first drug administration until the last drug intake + 28 days REP, up to 92.6 weeks

End point values	DBP+OLNP: Randomised to placebo	DBP+OLNP: Randomised to Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Placebo DBP+OLNP: 1st till last Placebo intake (DBP), up to 24.4 weeks + 28 days (REP) and 1st till last Nintedanib intake (OLNP), up to 64.6 weeks + 28 days (REP).

Nintedanib DBP+OLNP: 1st till last Nintedanib intake, up to 85.1 weeks + 28 days (REP).

Adverse event reporting additional description:

Treated set (TS): The TS consisted of subjects who were randomised to a treatment group and received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	DBP: Randomised to placebo

Reporting group description:

This arm shows placebo randomised subjects treated orally with a Nintedanib matching placebo soft capsule twice daily with a dose interval of approximately 12 hours from one dose to the next dose in the double-blind period (DBP). Medication dosage was per administration 50 milligram (mg) [2 capsules with strength 25 mg],75 mg [3 capsules with strength 25 mg], 100 mg [1 capsule with strength 100 mg or 4 capsules with strength 25 mg] or 150 mg [1 capsule with strength 150 mg or 6 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. In this arm subjects received placebo only (DBP). DBP: Planned was from first randomised trial drug intake to last blinded drug intake.

Reporting group title	DBP+OLNP: Randomised Nintedanib (Nintedanib exposure period)

Reporting group description:

This arm shows Nintedanib randomised subjects treated orally with Nintedanib in the DBP and OLNP twice daily with a dose interval of approximately 12 hours from one dose to the next dose. Medication dosage was per administration 50 milligram (mg) [2 capsules with strength 25 mg],75 mg [3 capsules with strength 25 mg], 100 mg [1 capsule with strength 100 mg or 4 capsules with strength 25 mg] or 150 mg [1 capsule with strength 150 mg or 6 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. In this arm subjects received Nintedanib in both periods (DBP + OLNP). Subjects in this arm do not entail subjects from the 'randomised to placebo' arms. DBP: Planned was from first randomised trial drug intake to last blinded drug intake. OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Reporting group title	OLNP: Randomised to placebo and switched to Nintedanib

Reporting group description:

This arm shows subjects who continued with the open-label Nintedanib period (OLNP) after the DBP, switched to active Nintedanib treatment in the OLNP and were treated orally with Nintedanib twice daily with a dose interval of approximately 12 hours from one dose to the next dose. Medication dosage was per administration 50 milligram (mg) [2 capsules with strength 25 mg],75 mg [3 capsules with strength 25 mg], 100 mg [1 capsule with strength 100 mg or 4 capsules with strength 25 mg] or 150 mg [1 capsule with strength 150 mg or 6 capsules with strength 25 mg] based on the subject's weight at baseline (= 0 weeks). The dosage was adjusted at subsequent visits if the subject's weight had changed. In this arm subjects received Nintedanib only (OLNP). OLNP: Planned was from first open-label Nintedanib intake to last open-label Nintedanib intake.

Serious adverse events	DBP: Randomised to placebo	DBP+OLNP: Randomised Nintedanib (Nintedanib exposure period)	OLNP: Randomised to placebo and switched to Nintedanib
Total subjects affected by serious			

adverse events			
subjects affected / exposed	1 / 13 (7.69%)	5 / 26 (19.23%)	2 / 11 (18.18%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Carbon dioxide increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Neurogenic shock			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Frontal lobe epilepsy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Tooth development disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			

	subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 11 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress				
	subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 11 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations				
COVID-19				
	subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 11 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	DBP: Randomised to placebo	DBP+OLNP: Randomised Nintedanib (Nintedanib exposure period)	OLNP: Randomised to placebo and switched to Nintedanib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 13 (84.62%)	26 / 26 (100.00%)	11 / 11 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	2 / 11 (18.18%)
occurrences (all)	0	2	3
Fatigue			
subjects affected / exposed	2 / 13 (15.38%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	3	2	0
Pain			

subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	4 / 26 (15.38%)	1 / 11 (9.09%)
occurrences (all)	1	6	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Multiple allergies			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	3 / 11 (27.27%)
occurrences (all)	1	0	3
Dyspnoea exertional			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	2 / 13 (15.38%)	0 / 26 (0.00%)	2 / 11 (18.18%)
occurrences (all)	3	0	2
Rhinorrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 13 (15.38%)	1 / 26 (3.85%)	2 / 11 (18.18%)
occurrences (all)	2	2	2
Nasal congestion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Bruxism			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	2 / 11 (18.18%)
occurrences (all)	0	1	3
Weight decreased			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
X-ray limb abnormal			
subjects affected / exposed	2 / 13 (15.38%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Burns second degree			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Supernumerary teeth			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

Right atrial hypertrophy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	2 / 11 (18.18%)
occurrences (all)	2	5	2
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 13 (23.08%)	6 / 26 (23.08%)	4 / 11 (36.36%)
occurrences (all)	4	9	5
Abdominal pain upper			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	0 / 11 (0.00%)
occurrences (all)	4	3	0
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Dental caries			
subjects affected / exposed	3 / 13 (23.08%)	7 / 26 (26.92%)	1 / 11 (9.09%)
occurrences (all)	3	27	2
Dental cyst			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	12 / 26 (46.15%)	6 / 11 (54.55%)
occurrences (all)	2	26	7
Dyspepsia			

subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	6	0	1
Faeces soft			
subjects affected / exposed	2 / 13 (15.38%)	1 / 26 (3.85%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Malpositioned teeth			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	0 / 11 (0.00%)
occurrences (all)	1	4	0
Nausea			
subjects affected / exposed	3 / 13 (23.08%)	6 / 26 (23.08%)	6 / 11 (54.55%)
occurrences (all)	3	7	12
Paraesthesia oral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Tooth development disorder			
subjects affected / exposed	1 / 13 (7.69%)	6 / 26 (23.08%)	0 / 11 (0.00%)
occurrences (all)	1	6	0
Tooth deposit			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Tooth disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Tooth impacted			
subjects affected / exposed	2 / 13 (15.38%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	4	7	0
Vomiting			
subjects affected / exposed	3 / 13 (23.08%)	7 / 26 (26.92%)	4 / 11 (36.36%)
occurrences (all)	3	21	17
Skin and subcutaneous tissue disorders			

Melanosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	1	3	0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 13 (7.69%)	7 / 26 (26.92%)	1 / 11 (9.09%)
occurrences (all)	1	7	1
Gastrointestinal bacterial overgrowth			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	4 / 26 (15.38%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	1 / 11 (9.09%)
occurrences (all)	0	1	2
Respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			

subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	2 / 11 (18.18%)
occurrences (all)	2	2	2
Tooth abscess			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	1 / 11 (9.09%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2020	This amendment was implemented after the first patient was enrolled into the trial. The following main changes were introduced: •The unblinding of selected non-trial personnel from the sponsor involved in the PK analysis was further specified based on the Food and Drug Administration (FDA) recommendation to conduct an interim PK evaluation at Week 2 post-dose to ensure that the systemic exposure of nintedanib with the proposed weight-based dosing regimen in patients of 6 to 17 years of age is comparable with adults. •It was clarified that SMC members were independent from the trial team and that the SMC reviewed PK data in addition to safety data. Furthermore, the actions expected from the SMC to mitigate the risk in the trial were specified in more detail. •Based on an FDA recommendation, restrictions regarding concomitant use of potent Pgp and CYP3A4 inhibitors and inducers were added to minimise potential impact of these co-medications on the primary PK endpoint. •Exclusion criterion No. 13 was modified to exclude patients with documented allergy to soya to align with the contraindications reported in the Investigator's Brochure. •Results from the trial in adults with PF-ILD were added, as they had become available. It was clarified that if PK data for the primary analysis were not sufficient at the time of DBL1, further PK data were to be collected. •It was specified that conduct of MRI/x-ray, dental examination, and dental imaging was to only be done in patients who qualified for randomisation in order to avoid unnecessary procedures.
14 June 2021	Following main changes were introduced by this amendment: •First dose of open-label trial medication of Part B (Visit 6) was administered at trial site to ensure monitoring of immediate adverse reactions to those patients who had received placebo during Part A and received their first dose of active medication at Visit 6. •Clarified laboratory tests with clinically relevant changes at EoT were repeated. •Follow-up Visit time window was reduced from 7 to 3 days. •PK sampling was repeated if blood samples were not taken at required time point, wrong medication was taken, a sample was destroyed/lost during shipment to obtain all required samples for PK analyses, if possible. •Information about reported adverse reactions and risks specific for paediatric population was added.•Mitigation measures to address additional risks due to COVID-19 pandemic were added. If site access was restricted, some activities on site such as on-site source data review and source data verification was performed remotely or replaced by centralised monitoring. No restrictions for trial participants to receive COVID-19 vaccination. •PK sampling in 10 children aged 6 to 11 years was completed at DBL1, if feasible. •If further PK data were needed at DBL1 snapshot was taken once further PK data had been collected and data based on DBL1 snapshot was updated and trial team was informed about number of patients with evaluable PK missing to reach target. •Specified procedures if patient's weight decrease below 13.5 kg. •Pathological findings in bone imaging and stunted growth in dental imaging were added to list of AESIs •Instructions on treatment interruption and resumption of treatment. •Primary PK analysis was calculated by non-compartmental and compartmental analysis. Clarified Investigational Medicinal Product (IMP) interruption was at most 4 weeks, while re-escalation to dose assigned could occur any time per investigator judgement. •SMC was to have no contact with central readers.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	Subject recruitment and trial site initiation were paused due to the Covid-19 pandemic.	04 June 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The end of trial (EoT) was planned in the protocol once 30 subjects had completed pharmacokinetic sampling at Week 26 or prematurely discontinued the trial.
At EoT no subject had reached Week 100 yet. The trial was completed as per protocol.

Notes: