Clinical trial results:
An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD-ON)

Summary

EudraCT number	2020-005554-23
Trial protocol	CZ ES PL HU BE NL GR DE FR PT FI DK IT NO
Global end of trial date	13 August 2025

Results information

Result version number	v1 (current)
This version publication date	28 February 2026
First version publication date	28 February 2026

Trial information

Trial identification

Sponsor protocol code	1199-0378

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05285982
WHO universal trial number (UTN)	U1111-1305-7514
Other trial identifiers	CTIS: 2024-515743-27-00

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, 1 018002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 1 018002430127, 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	18 September 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 August 2025
Global end of trial reached?	Yes
Global end of trial date	13 August 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the safety and tolerability of long-term treatment with nintedanib in paediatric patients with clinically significant fibrosing interstitial lung disease (ILD).

Protection of trial subjects:

The patient’s legally accepted representative (and/or the patient, where applicable) were informed that they were free to withdraw their consent (or assent, where applicable) at any time during the trial without penalty or prejudice.
Whenever feasible and for roll-over patients only, the first visits (Visit 1 and 2) of trial 1199-0378 were to occur on the same day as the end-of-treatment (EoT) Visit of trial 1199-0337 to allow for continuous treatment. In this case, procedures performed at the EoT of trial 1199-0337 were not to be repeated as part of Visit 1 or 2 in trial 1199-0378. Nintedanib dose could be interrupted/reduced without interruption at discretion of investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 April 2022
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	Argentina: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Finland: 1

Worldwide total number of subjects	70
EEA total number of subjects	30

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)	20
Adolescents (12-17 years)	45
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pediatric patients with clinically significant fibrosing Interstitial Lung Disease who completed the parent trial 1199-0337 or new patients who were eligible to enter this trial.

Pre-assignment

Screening details:

Only subjects that met all study eligibility criteria were to be entered. They were free to withdraw at any time for any reason given. Close monitoring was adhered to throughout trial conduct.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Nintedanib

Arm description:

Pediatric patients with clinically significant fibrosing intestitial lung disease (ILD) who either completed the parent trial 1199-0337 or were new patients received nintedanib soft gelatine capsules. Nintedanib doses ranged from 50 milligrams (mg) bid (13.5 to < 23 kilograms (kg) bodyweight) to 150 mg bid (>=57.5 kg bodyweight).

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:

Nintedanib doses ranged from 50 milligrams (mg) bid (13.5 to <23 kilograms (kg) bodyweight) to 150 mg bid (>=57.5 kg bodyweight).

Number of subjects in period 1[1]	Nintedanib
Started	54
Completed	30
Not completed	24
Adverse event, serious fatal	1
Other treatment option available	2
Adverse event, non-fatal	6
Perceived lack of efficacy	2
Burden of trial procedures	2
Change of residence	1
Other than listed	9
No reason provided	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of the 70 subjects enrolled, 54 started the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib
Reporting group description:	
Pediatric patients with clinically significant fibrosing intestitial lung disease (ILD) who either completed the parent trial 1199-0337 or were new patients received nintedanib soft gelatine capsules. Nintedanib doses ranged from 50 milligrams (mg) bid (13.5 to < 23 kilograms (kg) bodyweight) to 150 mg bid (>=57.5 kg bodyweight).	

Reporting group values	Nintedanib	Total	
Number of subjects	54	54	
Age categorical			
Treated Set (TS): The TS included all patients who were administered at least 1 dose of trial medication.			
Units: Participants			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	14	14	
Adolescents (12-17 years)	35	35	
Adults (18-64 years)	5	5	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Treated Set (TS): The TS included all patients who were administered at least 1 dose of trial medication.			
Units: years			
arithmetic mean	13.6		
standard deviation	± 3.3	-	
Sex: Female, Male			
Treated Set (TS): The TS included all patients who were administered at least 1 dose of trial medication.			
Units: Participants			
Female	33	33	
Male	21	21	
Race (NIH/OMB)			
Treated Set (TS): The TS included all patients who were administered at least 1 dose of trial medication.			
Units: Subjects			
American Indian or Alaska Native	3	3	
Asian	2	2	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	6	6	
White	41	41	
More than one race	1	1	
Unknown or Not Reported	1	1	
Ethnicity (NIH/OMB)			
Treated Set (TS): The TS included all patients who were administered at least 1 dose of trial medication.			
Units: Subjects			
Hispanic or Latino	16	16	

Not Hispanic or Latino	37	37	
Unknown or Not Reported	1	1	

End points

End points reporting groups

Reporting group title	Nintedanib

Reporting group description:

Pediatric patients with clinically significant fibrosing intestitial lung disease (ILD) who either completed the parent trial 1199-0337 or were new patients received nintedanib soft gelatine capsules. Nintedanib doses ranged from 50 milligrams (mg) bid (13.5 to < 23 kilograms (kg) bodyweight) to 150 mg bid (>=57.5 kg bodyweight).

Primary: Number of patients with treatment-emergent adverse events (AEs) over the whole trial

End point title	Number of patients with treatment-emergent adverse events (AEs) over the whole trial[1]

End point description:

Number of patients with treatment-emergent adverse events (AEs) over the whole trial.

Treated Set (TS): The TS included all patients who were administered at least 1 dose of trial medication.

End point type	Primary

End point timeframe:

From first drug administration until end of residual effect period (REP) 28 days after the last dose of trial medication, up to 1127 days.

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: The endpoint was only analysed descriptively.

End point values	Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Participants	53			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until end of residual effect period (REP) 28 days after the last dose of trial medication, up to 1127 days.

Adverse event reporting additional description:

Treated Set (TS): The TS included all patients who were administered at least 1 dose of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	28.0

Reporting groups

Reporting group title	Total

Reporting group description: -

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 54 (44.44%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Teratoma			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Transplant rejection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Pulmonary cavitation			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications			
Post procedural complication			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Sickle cell anaemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Right ventricular failure			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Guillain-Barre syndrome			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Optic atrophy			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric fistula			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal hypomotility			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth development disorder			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder rupture				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteonecrosis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Respiratory tract infection				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Skin infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 54 (98.15%)		
Investigations			
Weight decreased			
subjects affected / exposed	8 / 54 (14.81%)		
occurrences (all)	11		
Hepatic enzyme increased			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	7		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 54 (24.07%)		
occurrences (all)	24		
Dizziness			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	5		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	12		

Chest pain subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Fatigue subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	26 / 54 (48.15%) 63		
Nausea subjects affected / exposed occurrences (all)	17 / 54 (31.48%) 32		
Abdominal pain subjects affected / exposed occurrences (all)	10 / 54 (18.52%) 17		
Vomiting subjects affected / exposed occurrences (all)	21 / 54 (38.89%) 60		
Dental caries subjects affected / exposed occurrences (all)	16 / 54 (29.63%) 33		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Constipation subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 5		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 4		
Respiratory, thoracic and mediastinal disorders			

Nasal congestion subjects affected / exposed occurrences (all)	7 / 54 (12.96%) 10		
Cough subjects affected / exposed occurrences (all)	16 / 54 (29.63%) 22		
Epistaxis subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 4		
Interstitial lung disease subjects affected / exposed occurrences (all)	6 / 54 (11.11%) 6		
Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 54 (11.11%) 6		
Dyspnoea subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 7		
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 8		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Musculoskeletal and connective tissue disorders Back pain			

subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Arthralgia			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Infections and infestations			
Viral infection			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	12 / 54 (22.22%)		
occurrences (all)	22		
Respiratory tract infection			
subjects affected / exposed	9 / 54 (16.67%)		
occurrences (all)	17		
Nasopharyngitis			
subjects affected / exposed	11 / 54 (20.37%)		
occurrences (all)	17		
COVID-19			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	9		
Bronchitis			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	11		
Rhinitis			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pneumonia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	9		
Influenza			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	9		
Gastroenteritis viral			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	6		

Gastroenteritis subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2022	In addition to minor corrections and clarification, the following main changes were introduced: • The trial rationale was defined specifically for new and roll-over patients (instead of all patients combined). • Per protocol, a transition period of 8 weeks was allowed. In Protocol Amendment 1, it was clarified that patients from trial 1199-0337 who were eligible for roll-over but had a transition period of more than 12 weeks were considered as 'new patients' in this trial. Furthermore, it was specified which inclusion and exclusion criteria applied to this subcategory of new patients. Patients with a transition period of more than 8 weeks, but up to 12 weeks were still considered roll-over patients, but this deviation was to be documented as individual protocol deviation (iPD). • The minimum treatment duration for new patients was changed from 'a minimum of 2 years' to 'until the end of trial or until alternative treatment options become available' in order to reflect the staggered enrolment of new patients. The overall end of trial was defined accordingly and the second interim analysis was removed. • A time window of +7 days was added for the follow-up/End of Study (EoS) Visit. • The time windows for follow-up bone imaging, dental imaging, and dental examination were revised to allow for some flexibility without compromising patient safety. • After a previous switch to smaller capsules, it was permitted to switch back to larger capsules (i.e., from 25 milligram (mg) to 100 mg capsules). • It was clarified that female partners of male patients did not have to follow the contraceptive guidelines. • To support the overall safety assessment, the possibility of review of bone and dental images by an external expert was added. Furthermore, a mandatory review of all dental findings of stunted growth as well as an optional review of other dental findings by the Adjudication Committee (AC) was added.
18 April 2023	In addition to minor corrections and clarifications, the following main changes were introduced: • The allowed time windows for follow-up bone imaging, dental imaging, and dental examination were further clarified. In addition, a one-time pre-or postponement of an assessment by 2 months was allowed to allow for alignment of bone imaging and dental imaging/examination with the regular trial site visits. • In order to limit the burden for a patient without compromising on patient safety, the number of follow-up bone and dental imaging assessments was limited to 1 after End of Treatment (EoT). • The further endpoints 'change from baseline in sitting height' and 'change from baseline in leg length' were removed due to inconsistencies in the measurements, which would impact data comparability.

29 November 2023	In addition to minor corrections and clarifications, the following main changes were introduced: • As agreed with European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP), trial 1199-0378 was extended by an additional year of treatment, i.e., maximum treatment duration for roll-over patients was changed from 2 to 3 years. Four additional clinical visits were added during this extra year and timepoints of trial assessments were adapted accordingly. • As nintedanib is available for adult patients outside of the trial, patients should complete the trial before their 22nd birthday. • The possibility to collect information on age of menarche (for female patients only) and nutritional support was added. • Clarified that bone imaging follow-up procedures for patients aged 19 and older were only required on an annual basis. • New patients were approached in a way that would increase the collection of long-term data until the end of trial. • Additional timepoints were added for selected further endpoints (i.e., incidence of treatment-emergent pathological findings of epiphyseal growth plate on imaging and dental examination or imaging, length of hospitalisation) due to prolongation of trial treatment. • The possibility to restart trial treatment after pregnancy was added.
15 April 2024	This amendment was introduced to harmonise the Clinical Trial Protocol (CTP) for the transition to European Union (EU) Clinical Trials Regulation. The amendment included local amendments already approved in concerned countries (the first 3 bullets) as well as a new change (the last bullet): • As requested by French Health Authority (ANSM), trial population in France was limited to adolescents 12 to 17 years old at Visit 2. This change was introduced to Local Amendment 1 France (dated 05 Jul 2021) and approved by the local regulatory body prior to the global protocol harmonisation. • As requested by Polish authorities and Norwegian Medicines Agency, the frequency of the pregnancy test for female patients in Poland and Norway was revised to every 4 weeks. This change was introduced to Local Amendment 1 Poland (dated 09 Jul 2021) and Local Amendment 1 Norway (dated 19 Feb 2022) and approved by the respective local regulatory bodies prior to the global protocol harmonisation. • As requested by Norwegian Medicines Agency, Visit 3a was also applicable for new patients in Norway and had to be performed at Week 6 (Day 43). This change was introduced to Local Amendment 1 Norway (dated 19 Feb 2022) and approved by the respective local regulatory body prior to the global protocol harmonisation. • Several trial conducts were allowed to limit the burden for patients, e.g., replacing the End of Study (EoS) Visit with a phone call if patients were not able to visit sites for medical reasons, allowing the follow-up visit to be skipped if the End of Treatment (EoT) Visit was delayed and performed 28 days or more after treatment discontinuation.
27 November 2024	In addition to minor corrections and clarifications, the following main changes were introduced: • Clarified that the overall end of trial was to take place approximately when last roll-over patient was expected to reach 3 years of treatment. • As requested by Italian Health Authority, the frequency of the pregnancy test was revised to every 4 weeks for female patients in all countries. • Shortened the follow-up duration for urine pregnancy test for female patients who continued visits off treatment to limit the burden for patients. • Following regulatory interactions, additional timepoints were added for selected further safety endpoints, i.e., change in height from baseline, change in height-for-age z-score (ΔHAZ), change in weight-for-age z-score (ΔWAZ), and change in body mass index-for-age z-score (ΔBAZ).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Some limitations due to the nature of the extension trial should be considered when interpreting the data (i.e. bias in the selection of the population and no comparative arm). All endpoints were considered exploratory only.

Notes: