Clinical trial results:
Long-term phase IV multicenter study on the safety and efficacy of Omnitrope® (rhGH) in short children born Small for Gestational Age (SGA)

Summary

EudraCT number	2006-002506-58
Trial protocol	HU DE CZ PL BE
Global end of trial date	25 March 2022

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	CEP00-401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00537914
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	25 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the long-term effect of growth hormone treatment on the development of diabetes in short children born SGA during treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 213
Country: Number of subjects enrolled	Georgia: 20
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Belgium: 1
Worldwide total number of subjects	278
EEA total number of subjects	258

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)	253
Adolescents (12-17 years)	25
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was carried out in 31 centers in 7 countries (Poland, Romania, Hungary, Czech Republic, Germany, Belgium and Georgia).

Pre-assignment

Screening details:

This study was not randomized. All enrolled patients received Omnitrope

Period 1

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

Arms

Arm title	Omnitrope

Arm description:

All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	EP2000
Other name	Omnitrope
Pharmaceutical forms	Solution for injection, Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.

Number of subjects in period 1	Omnitrope
Started	278
Full analysis set (FAS)	278
Safety analysis set (SAS)	277
Completed	166
Not completed	112
Adverse event, serious fatal	1
Treatment failure	10
Adverse event, non-fatal	7
patients documented other	16
Lost to follow-up	19
Withdrawal of informed consent	59

Baseline characteristics

Reporting groups	
Reporting group title	Omnitrope
Reporting group description:	
All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.	

Reporting group values	Omnitrope	Total	
Number of subjects	278	278	
Age categorical Units: Subjects			
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)	253	253	
Adolescents (12-17 years)	25	25	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	7.36		
standard deviation	± 2.70	-	
Sex: Female, Male Units: Participants			
Female	130	130	
Male	148	148	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	276	276	
Oriental	1	1	
Mixed ethnic origin (Arabic/ Caucasian)	1	1	
Black	0	0	

End points

End points reporting groups

Reporting group title	Omnitrope

Reporting group description:

All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.

Primary: Number of participants with development of diabetes in short children born SGA during treatment

End point title	Number of participants with development of diabetes in short children born SGA during treatment[1]

End point description:

The development of diabetes in short children born SGA during treatment was evaluated based on the carbohydrate metabolism parameters FPG, HbA1c and OGTT (basal and 2-h plasma glucose). Only cases which were confirmed by the investigator were included.

End point type	Primary

End point timeframe:

throughout the study, approximately 13 years

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: No statistical analysis were performed for this outcome

End point values	Omnitrope			
Subject group type	Reporting group			
Number of subjects analysed	277			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Height (H) (cm) from baseline

End point title	Mean change in Height (H) (cm) from baseline

End point description:

Mean change in Height from baseline for all patients was reported.

End point type	Secondary

End point timeframe:

Baseline, 1 year, 2 years, 5 years and 9 years

End point values	Omnitrope			
Subject group type	Reporting group			
Number of subjects analysed	278			
Units: cm				
arithmetic mean (confidence interval 95%)				
1 year	9.08 (8.89 to 9.27)			
2 years	16.52 (16.22 to 16.82)			
5 years	35.10 (34.48 to 35.72)			
9 years	58.07 (56.83 to 59.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Height standard deviation score over time (H SDS) from baseline

End point title	Mean change in Height standard deviation score over time (H SDS) from baseline

End point description:

Mean change in Height standard deviation score over time (H SDS) from baseline was reported.

End point type	Secondary

End point timeframe:

Baseline, 3 months, 0.5 year, 9 months, 1 year, 1.25 years, 1.5 years, 1.75 years, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 12.5 years

End point values	Omnitrope			
Subject group type	Reporting group			
Number of subjects analysed	278			
Units: cm				
arithmetic mean (confidence interval 95%)				
3 months	0.30 (0.28 to 0.33)			
0.5 year	0.51 (0.47 to 0.54)			
9 months	0.68 (0.64 to 0.72)			
1 year	0.81 (0.76 to 0.86)			
1.25 years	0.93 (0.87 to 0.98)			
1.5 years	1.04 (0.98 to 1.10)			
1.75 years	1.16 (1.09 to 1.22)			

2 years	1.25 (1.18 to 1.31)			
3 years	1.50 (1.42 to 1.58)			
4 years	1.67 (1.57 to 1.77)			
5 years	1.82 (1.70 to 1.94)			
6 years	1.94 (1.81 to 2.07)			
7 years	2.07 (1.92 to 2.22)			
8 years	2.19 (2.03 to 2.35)			
9 years	2.18 (1.99 to 2.37)			
10 years	2.21 (2.00 to 2.43)			
11 years	2.38 (2.13 to 2.63)			
12 years	2.39 (1.81 to 2.97)			
12.5 years	3.01 (1.78 to 4.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Height velocity (HV) (cm/year) over time from baseline

End point title	Mean change in Height velocity (HV) (cm/year) over time from baseline
End point description:	
Mean change in Height velocity (HV) (cm/year) over time from baseline was reported.	
End point type	Secondary
End point timeframe:	
Baseline, 1 year, 2 years, 5 years and 9 years	

End point values	Omnitrope			
Subject group type	Reporting group			
Number of subjects analysed	278			
Units: cm/year				
arithmetic mean (confidence interval 95%)				
1 year	4.71 (4.47 to 4.96)			
2 years	3.02 (2.80 to 3.25)			
5 years	1.37 (1.01 to 1.73)			
9 years	0.10 (-0.53 to 0.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Height velocity standard deviation score (HV SDS) over time from baseline

End point title	Mean change in Height velocity standard deviation score (HV SDS) over time from baseline

End point description:

Mean change in Height velocity standard deviation score (HV SDS) over time from baseline was reported.

End point type	Secondary

End point timeframe:

Baseline, Baseline, 3 months, 0.5 year, 9 months, 1 year, 1.25 years, 1.5 years, 1.75 years, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 12.5 years

End point values	Omnitrope			
Subject group type	Reporting group			
Number of subjects analysed	278			
Units: cm/year				
arithmetic mean (confidence interval 95%)				
3 months	8.41 (7.76 to 9.07)			
0.5 year	7.27 (6.83 to 7.71)			
9 months	6.69 (6.31 to 7.06)			
1 year	6.26 (5.92 to 6.59)			
1.25 years	5.29 (4.99 to 5.60)			
1.5 years	4.85 (4.55 to 5.15)			
1.75 years	4.59 (4.28 to 4.91)			
2 years	4.35 (4.02 to 4.68)			
3 years	3.62 (3.23 to 4.00)			
4 years	3.08 (2.68 to 3.47)			
5 years	2.99 (2.50 to 3.49)			
6 years	2.63 (2.14 to 3.13)			
7 years	2.43 (1.95 to 2.92)			

8 years	1.37 (0.75 to 1.98)			
9 years	0.85 (0.14 to 1.55)			
10 years	0.62 (-0.24 to 1.47)			
11 years	1.60 (0.36 to 2.84)			
12 years	1.34 (-0.50 to 3.18)			
12.5 years	1.98 (1.74 to 2.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in serum IGF-1 level (nmol/L) from baseline

End point title	Mean change in serum IGF-1 level (nmol/L) from baseline

End point description:

Mean change in serum IGF-1 level (nmol/L) from baseline was reported.

End point type	Secondary

End point timeframe:

Baseline, 1 year, 2 years, 5 years and 9 years

End point values	Omnitrope			
Subject group type	Reporting group			
Number of subjects analysed	278			
Units: nmol/L				
arithmetic mean (confidence interval 95%)				
1 year	20.58 (18.77 to 22.39)			
2 years	30.64 (28.16 to 33.12)			
5 years	44.87 (41.33 to 48.40)			
9 years	75.72 (69.59 to 81.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in IGFBP-3 levels (nmol/L) from baseline

End point title	Mean change in IGFBP-3 levels (nmol/L) from baseline

End point description: Mean change in IGFBP-3 levels (nmol/L) from baseline was reported.	
End point type	Secondary
End point timeframe: Baseline, 1 year, 2 years, 5 years and 9 years	

End point values	Omnitrope			
Subject group type	Reporting group			
Number of subjects analysed	278			
Units: nmol/L				
arithmetic mean (confidence interval 95%)				
1 year	30.48 (27.04 to 33.92)			
2 years	48.48 (44.51 to 52.45)			
5 years	92.94 (87.65 to 98.23)			
9 years	139.12 (126.12 to 152.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the development of anti-rhGH antibodies during Omnitrope treatment

End point title	Number of participants with the development of anti-rhGH antibodies during Omnitrope treatment
End point description: Number of participants with the development of anti-rhGH antibodies with positive test result were reported.	
End point type	Secondary
End point timeframe: throughout the study, approximately 13 years	

End point values	Omnitrope			
Subject group type	Reporting group			
Number of subjects analysed	277			
Units: Participants	23			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment to end of the study i.e. up to 13 years.

Adverse event reporting additional description:

Any signs or symptoms were collected from first dose of study treatment to end of the study i.e. up to 13 years.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Omnitrope

Reporting group description:

All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.

Serious adverse events	Omnitrope		
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 277 (26.71%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pachydermodactyly			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			

Asthenia				
subjects affected / exposed	2 / 277 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Face oedema				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Obstruction				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Reproductive system and breast disorders				
Testicular torsion				
subjects affected / exposed	2 / 277 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Intermenstrual bleeding				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acquired hydrocele				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Varicocele				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	7 / 277 (2.53%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 1		
Asthma			
subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nasal septum perforation			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Behaviour disorder			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Enuresis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac murmur			

subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Alcohol poisoning			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Facial bones fracture			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Head injury			
subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Foreign body in gastrointestinal tract			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Joint dislocation			
subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Internal injury			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ligament sprain			

subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multiple injuries				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Procedural complication				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Radius fracture				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Road traffic accident				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skull fracture				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sternal fracture				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Toxicity to various agents				
subjects affected / exposed	2 / 277 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Traumatic shock				

subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Upper limb fracture			
subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Congenital, familial and genetic disorders			
Congenital arterial malformation			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Developmental hip dysplasia			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gilbert's syndrome			
subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Ventricular arrhythmia			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coma			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Intellectual disability			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Seizure			
subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Headache			
subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Anaemia			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thrombocytopenia			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Abdominal pain upper			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aphthous ulcer			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chronic gastritis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Duodenal ulcer			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dysphagia			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Eosinophilic oesophagitis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastritis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Inguinal hernia			

subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Malabsorption			
subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Vomiting			
subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vitiligo			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Urethral fistula			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nephrolithiasis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Haematuria				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urinary incontinence				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urinary retention				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urethral stenosis				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Endocrine disorders				
Precocious puberty				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Musculoskeletal and connective tissue disorders				
Arthritis				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Scoliosis				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Osteonecrosis				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Infections and infestations			
Appendicitis			
subjects affected / exposed	4 / 277 (1.44%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Bronchitis			
subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Bacterial sepsis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ear infection			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Epididymitis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis			
subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Giardiasis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Helicobacter infection			
subjects affected / exposed	2 / 277 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Infectious mononucleosis			

subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Laryngitis				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Orchitis				
subjects affected / exposed	2 / 277 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Otitis media				
subjects affected / exposed	4 / 277 (1.44%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Otitis media acute				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Otitis media chronic				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Peritonitis				
subjects affected / exposed	1 / 277 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pharyngitis				
subjects affected / exposed	2 / 277 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia				

subjects affected / exposed	3 / 277 (1.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Rhinitis			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subcutaneous abscess			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hyperglycaemia			
subjects affected / exposed	1 / 277 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Omnitrope		
Total subjects affected by non-serious adverse events subjects affected / exposed	210 / 277 (75.81%)		
Investigations Insulin-like growth factor increased subjects affected / exposed occurrences (all)	9 / 277 (3.25%) 16		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	27 / 277 (9.75%) 49		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	23 / 277 (8.30%) 42		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) Seasonal allergy subjects affected / exposed occurrences (all)	11 / 277 (3.97%) 16 9 / 277 (3.25%) 12		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	10 / 277 (3.61%) 18 10 / 277 (3.61%) 10 21 / 277 (7.58%) 27 13 / 277 (4.69%) 24		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	20 / 277 (7.22%)		
occurrences (all)	56		
Rhinorrhoea			
subjects affected / exposed	14 / 277 (5.05%)		
occurrences (all)	26		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	12 / 277 (4.33%)		
occurrences (all)	15		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	27 / 277 (9.75%)		
occurrences (all)	32		
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	12 / 277 (4.33%)		
occurrences (all)	12		
Infections and infestations			
Bronchitis			
subjects affected / exposed	58 / 277 (20.94%)		
occurrences (all)	104		
Ear infection			
subjects affected / exposed	14 / 277 (5.05%)		
occurrences (all)	22		
Gastroenteritis			
subjects affected / exposed	11 / 277 (3.97%)		
occurrences (all)	12		
Influenza			
subjects affected / exposed	11 / 277 (3.97%)		
occurrences (all)	12		
Laryngitis			
subjects affected / exposed	9 / 277 (3.25%)		
occurrences (all)	15		
Nasopharyngitis			

subjects affected / exposed	78 / 277 (28.16%)			
occurrences (all)	302			
Otitis media				
subjects affected / exposed	19 / 277 (6.86%)			
occurrences (all)	35			
Otitis media acute				
subjects affected / exposed	9 / 277 (3.25%)			
occurrences (all)	13			
Pharyngitis				
subjects affected / exposed	92 / 277 (33.21%)			
occurrences (all)	310			
Rhinitis				
subjects affected / exposed	20 / 277 (7.22%)			
occurrences (all)	33			
Respiratory tract infection				
subjects affected / exposed	25 / 277 (9.03%)			
occurrences (all)	39			
Pneumonia				
subjects affected / exposed	17 / 277 (6.14%)			
occurrences (all)	21			
Scarlet fever				
subjects affected / exposed	11 / 277 (3.97%)			
occurrences (all)	12			
Upper respiratory tract infection				
subjects affected / exposed	47 / 277 (16.97%)			
occurrences (all)	119			
Tonsillitis				
subjects affected / exposed	35 / 277 (12.64%)			
occurrences (all)	86			
Sinusitis				
subjects affected / exposed	15 / 277 (5.42%)			
occurrences (all)	17			
Urinary tract infection				
subjects affected / exposed	17 / 277 (6.14%)			
occurrences (all)	20			
Varicella				

subjects affected / exposed	37 / 277 (13.36%)		
occurrences (all)	38		
Viral infection			
subjects affected / exposed	18 / 277 (6.50%)		
occurrences (all)	29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2007	- Change from EP2000 5 mg/ml lyophilized powder for solution for injection to EP2000 5 mg/1.5ml solution for injection - Reduction of blood glucose measurements - Recording of historical IGF-1 and IGFBP-3
27 November 2008	- Inclusion of subgroup analysis for different formulations - Allowing treatment of overweight children with SGA (deletion of exclusion criterion 7) - Safety reporting for device related events - Clarification of BA determination procedure
22 March 2012	- Introduction of a higher Omnitrope dose strength (10 mg/1.5 mL) - Discontinuation of anti-HCP antibody assessment
24 August 2017	- Addition of instructions for female patients of childbearing potential - Changes due to implementation of new processes and a new protocol template by the sponsor - Removal of the per-protocol population from analysis
07 February 2020	- The post-treatment observation EP00-402 (for patients who had been treated within this study, EP00-401) was terminated in 2018. All references to study EP00-402 were removed Clarification of the lost to follow up definition to limit protocol deviations and facilitate compliance to visit schedule

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported