



Clinical trial results:

Long-term safety follow-up after growth hormone Treatment (rhGH) of short children born Small for Gestational Age (SGA)

Summary

EudraCT number	2007-001364-72
Trial protocol	HU DE CZ PL
Global end of trial date	31 October 2018

Results information

Result version number	v1 (current)
This version publication date	15 May 2019
First version publication date	15 May 2019

Trial information

Trial identification

Sponsor protocol code	EP00-402
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01491854
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hexal AG / Sandoz
Sponsor organisation address	Industriestr. 25, Holzkirchen, Germany, 83807
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)	
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2018
Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to monitor short children born SGA who participated in study EP00-401 for the development of diabetes for a further 10 years after termination of rhGH treatment and to report the incidence of anti-rhGH antibodies (ADA) for 6 months after termination of rhGH 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	20 July 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Georgia: 9
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Poland: 91
Country: Number of subjects enrolled	Romania: 8
Worldwide total number of subjects	118
EEA total number of subjects	109

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)	13
Adolescents (12-17 years)	99
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

130 participants signed informed consent. Of the 130 enrolled subjects, 11 subjects had no post-baseline visit, leading to exclusion from the SAF/FAS. Another subject was excluded as he received treatment with Omnitrope, which was not consistent with the protocol. Accordingly, 118 subjects comprised the SAF and in the FAS

Pre-assignment

Screening details:

SAF : safety Analysis set

FAS : full Analysis set

Period 1

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

Blinding implementation details:

NA

Arms

Arm title	Monitoring of long-term safety
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Arm description:

Long-term safety follow-up after the end of treatment with Omnitrope (single arm)

Arm type	safety follow up
Investigational medicinal product name	omnitrope
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

not applicable : this was an observational follow-up study without intake of any investigational drug or control Treatment.

Investigational drug was given in EP00-401 trial, and the experimental product given in the EP00-401 is detailed here.

Number of subjects in period 1	Monitoring of long-term safety
Started	118
Completed	0
Not completed	118
Adverse event, serious fatal	1
Consent withdrawn by subject	2
mainly due early/premature termination	91
Lost to follow-up	24

Baseline characteristics

Reporting groups

Reporting group title	Monitoring of long-term safety
Reporting group description:	
Long-term safety follow-up after the end of treatment with Omnitrope (single arm)	

Reporting group values	Monitoring of long-term safety	Total	
Number of subjects	118	118	
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)	13	13	
Adolescents (12-17 years)	99	99	
Adults (18-64 years)	6	6	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	14.79		
standard deviation	± 2.848	-	
Sex: Female, Male			
Units: Subjects			
Female	64	64	
Male	54	54	
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	118	118	

End points

End points reporting groups

Reporting group title	Monitoring of long-term safety
Reporting group description:	
Long-term safety follow-up after the end of treatment with Omnitrope (single arm)	

Primary: Evaluate the long-term effect of growth hormone treatment on the development of diabetes after end of therapy.

End point title	Evaluate the long-term effect of growth hormone treatment on the development of diabetes after end of therapy. ^[1]
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End point description:

Number of participants diagnosed with Diabetes mellitus type 2 during the study, defined as fulfillment of these 3 criteria: - FPG $\geq$ 126 mg/dl (7.0 mmol/L) during blood sampling and/or during Oral Glucose Tolerance Test (OGTT) - 2-h plasma glucose $\geq$ 200 mg/dl (11.1 mmol/L) during an OGTT - Investigator documenting diagnosis of diabetes mellitus type 2 during OGTT

End point type	Primary
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End point timeframe:

5 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 analyses was performed

End point values	Monitoring of long-term safety			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: To evaluate the long term effects of rhGH on carbohydrate metabolism through fasting plasma glucose (FPG) Levels

End point title	To evaluate the long term effects of rhGH on carbohydrate metabolism through fasting plasma glucose (FPG) Levels ^[2]
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End point description:

Supportive to Primary Endpoint

End point type	Primary
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End point timeframe:

baseline, 6 months, 1 year, 5 years

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: No statistical analyses was performed

End point values	Monitoring of long-term safety			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: mmol/L				
arithmetic mean (standard deviation)				
FPG baseline	4.69 (± 0.492)			
FPG 6 months	-0.13 (± 0.567)			
FPG 1 year	-0.14 (± 0.457)			
FPG 5 years	-0.37 (± 0.856)			

Statistical analyses

No statistical analyses for this end point

Primary: To evaluate the long term effects of rhGH on carbohydrate metabolism through fasting Insulin levels

End point title	To evaluate the long term effects of rhGH on carbohydrate metabolism through fasting Insulin levels ^[3]
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End point description:

Supportive to Primary Endpoint

End point type	Primary
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End point timeframe:

baseline, 6 months, 1 year, 5 years

Notes:

[3] - 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 analyses was performed

End point values	Monitoring of long-term safety			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: pmol/L				
arithmetic mean (standard deviation)				
baseline	70.87 (± 38.477)			
6 months	-2.34 (± 38.267)			
1 year	-7.48 (± 34.676)			
5 years	3.40 (± 52.526)			

Statistical analyses

No statistical analyses for this end point

Primary: To evaluate the long term effects of rhGH on carbohydrate metabolism through glucose glycosylated hemoglobin (HbA1c)

End point title	To evaluate the long term effects of rhGH on carbohydrate metabolism through glucose glycosylated hemoglobin (HbA1c) ^[4]
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End point description:

Supportive to Primary Endpoint

End point type	Primary
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End point timeframe:

baseline, 6 months, 1 year, 5 years

Notes:

[4] - 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 analyses was performed

End point values	Monitoring of long-term safety			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: percentage				
arithmetic mean (standard deviation)				
baseline	5.280 (± 0.3569)			
6 months	-0.057 (± 0.3621)			
1 year	-0.108 (± 0.2931)			
5 years	-0.308 (± 0.6036)			

Statistical analyses

No statistical analyses for this end point

Primary: To evaluate the long term effects of rhGH on carbohydrate metabolism through HOMA and QUICKI scores

End point title	To evaluate the long term effects of rhGH on carbohydrate metabolism through HOMA and QUICKI scores ^[5]
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End point description:

Supportive to Primary Endpoint. HOMA = homeostasis model assessment for Insulin resistance: Healthy Range: 1.0 (0.5–1.4). < 1.0 means you are insulin-sensitive which is optimal. > 1.9 indicates early insulin resistance. > 2.9 indicates significant insulin resistance. The quantitative insulin sensitivity check index (QUICKI) measures insulin sensitivity, which is the inverse of insulin resistance. The QUICKI calculation for insulin resistance in humans fall broadly within a range between 0.45 for unusually healthy individuals and 0.30 in diabetics. Lower numbers reflect greater insulin resistance.

End point type	Primary
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End point timeframe:

baseline, 6 months, 1 year, 5 years

Notes:

[5] - 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 analyses was performed

End point values	Monitoring of long-term safety			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: score on a scale				
arithmetic mean (standard deviation)				
HOMA score baseline	2.082 ($\pm$ 1.0336)			
HOMA score 6 months	-0.073 ($\pm$ 1.1447)			
HOMA score 1 year	-0.206 ($\pm$ 1.0170)			
HOMA score 5 years	0.094 ($\pm$ 1.8835)			
QUICKI score baseline	0.354 ($\pm$ 0.0459)			
QUICKI score 6 months	0.004 ($\pm$ 0.0350)			
QUICKI score 1 year	0.012 ($\pm$ 0.0413)			
QUICKI score 5 years	0.022 ($\pm$ 0.0703)			

Statistical analyses

No statistical analyses for this end point

Secondary: to evaluate IGF-I and IGFBP-3 levels for 10 years after end of growth hormone treatment

End point title	to evaluate IGF-I and IGFBP-3 levels for 10 years after end of growth hormone treatment
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End point description:

End point type	Secondary
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End point timeframe:

baseline, 6 months, 1 year , 5 years

End point values	Monitoring of long-term safety			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: nmol/L				
arithmetic mean (standard deviation)				

IGF-1 baseline	67.42 ($\pm$ 31.137)			
IGF-1 6 months	48.42 ($\pm$ 20.002)			
IGF-1 1 year	46.28 ($\pm$ 21.555)			
IGF-1 5 years	44.60 ($\pm$ 16.035)			
IGFBP-3 baseline	211.12 ($\pm$ 49.523)			
IGFBP-3 6 months	187.79 ($\pm$ 42.999)			
IGFBP-3 1 year	186.59 ($\pm$ 47.246)			
IGFBP-3 5 years	180.00 ($\pm$ 26.470)			

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate the incidence of anti-rhGH antibodies after 6 months after termination of growth hormone treatment.

End point title	To evaluate the incidence of anti-rhGH antibodies after 6 months after termination of growth hormone treatment.
End point description:	number of participants with positive results for anti-drug antibody (ADA). Percentages indicated are calculated based on the total number of patients (118 participants).
End point type	Secondary
End point timeframe:	baseline, 6 months, 1 year, 5 years

End point values	Monitoring of long-term safety			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: participants				
baseline	0			
6 months	1			
1 year	0			
5 years	0			

Statistical analyses

No statistical analyses for this end point

Secondary: to evaluate final height

End point title	to evaluate final height
End point description:	
End point type	Secondary
End point timeframe:	
baseline, 6 months, 1 year, 5 years	

End point values	Monitoring of long-term safety			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: cm				
arithmetic mean (standard deviation)				
baseline	152.63 ($\pm$ 16.362)			
6 months	152.41 ($\pm$ 16.894)			
1 year	152.43 ($\pm$ 16.698)			
5 years	150.42 ($\pm$ 12.938)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

approximately 9 years

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Total
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Reporting group description:

Total

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 118 (6.78%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	2 / 118 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
With nerve paralysis			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiatus hernia			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oligomenorrhoea			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spondylolisthesis			

subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Chronic tonsillitis			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 118 (19.49%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 118 (2.54%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			

Acne subjects affected / exposed occurrences (all)	4 / 118 (3.39%) 4		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	4 / 118 (3.39%) 5		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 118 (5.93%) 12 5 / 118 (4.24%) 7 4 / 118 (3.39%) 4 4 / 118 (3.39%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2012	the main purpose of this amendment was to modify the inclusion criteria and the visit schedule and assessments
09 May 2012	This amendment aims to refrain from further assessment of host cell protein (HCP).
06 June 2013	This amendment aims to document changes regarding requirements for safety monitoring and harmonization of safety related sections in the protocol.

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.

The study was terminated prematurely in accordance with the request to close study EP00-402 "EMEA/H/C/000607/MEA 10.2" submitted to the EMA on 29-Mar-2018 and adopted by the EMA on 28-Jun-2018

Notes: