Clinical trial results:
Evolution of growth rate in children with growth retardation related to long-term glucocorticosteroid therapy and treated by Genotonorm

Summary

EudraCT number	2004-002992-17
Trial protocol	Outside EU/EEA
Global end of trial date	01 December 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	23 July 2015

Trial information

Trial identification

Sponsor protocol code	A6281271

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00163189
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov.inquiries@pfizer.com
Scientific contact	ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov.inquiries@pfizer.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	29 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show an increase in height after 3 years of growth hormone (GH) treatment. However subjects will be followed for up to 5 years of treatment. Height in standard deviation (SD) for chronological age (CA) after 3 years will be compared to Height in SD for CA before inclusion in the trial.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2005
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	France: 98
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	37
Adolescents (12-17 years)	60
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The reason 'Study Terminated by Sponsor' mentioned in the subject disposition indicates the termination of study at a site (due to Good Clinical Practice [CP] compliance issues) and does not reflect the overall status of study.

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	Genotonorm

Arm description:

Subjects received genotonorm administered weekly, divided into 7 daily subcutaneous injections for up to 60 months.

Arm type	Experimental
Investigational medicinal product name	Genotonorm
Investigational medicinal product code	
Other name	Recombinant somatropin
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 0.46 milligram per kilogram (mg/kg) of genotonorm (maximum dose not exceeding 50 microgram/kg/day (mcg/kg/day) for up to 60 months.

Number of subjects in period 1	Genotonorm
Started	98
Completed	35
Not completed	63
' Protocol Violation'	2
Consent withdrawn by subject	11
Did not meet continuation criterion	16
Death	3
Study terminated by sponsor	11
Unspecified	6
Lost to follow-up	1
' Adverse Event'	6
Lack of efficacy	7

Baseline characteristics

Reporting groups	
Reporting group title	Genotonorm
Reporting group description:	
Subjects received genotonorm administered weekly, divided into 7 daily subcutaneous injections for up to 60 months.	

Reporting group values	Genotonorm	Total	
Number of subjects	98	98	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	11.8		
standard deviation	± 3.2	-	
Gender categorical			
Units: Subjects			
Female	24	24	
Male	74	74	

End points

End points reporting groups

Reporting group title	Genotonorm

Reporting group description:

Subjects received genotonorm administered weekly, divided into 7 daily subcutaneous injections for up to 60 months.

Primary: Change From Baseline in Height Standard Deviation Score (SDS) for Chronological Age (CA) at Month 36: Full Analysis Population

End point title	Change From Baseline in Height Standard Deviation Score (SDS) for Chronological Age (CA) at Month 36: Full Analysis Population[1]

End point description:

Height was measured using a wall mounted device (example, Harpenden stadiometer). The standing height of the subject was measured two times and the mean of these measurements was recorded. Height SDS CA Yx = (height Yx – reference mean for CA Yx) / reference SD for CA Yx; Yx refers to the value at particular timepoint x. Height in SDS was calculated using Sempe reference means and SD for height. CA calculated as integer (Date of height measurement–Date of birth)/365.25*12. Full analysis set (FAS) included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Primary

End point timeframe:

Baseline, Month 36

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: Statistical analysis has been provided in the attachment.

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: Standard Deviation Score (SDS)				
arithmetic mean (standard deviation)				
Baseline (n=58)	-2.91 (± 1.19)			
Change at Month 36 (n=30)	0.8 (± 1.03)			

Attachments (see zip file)	Change in Height SDS for CA: FAS population/Statistical

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Height Standard Deviation Score (SD) for Chronological Age (CA) at Month 36: Per Protocol (PP) Population

End point title	Change From Baseline in Height Standard Deviation Score (SD) for Chronological Age (CA) at Month 36: Per Protocol (PP) Population[2]

End point description:

Height was measured using a wall mounted device (example, Harpenden stadiometer). The standing height of the subject was measured two times and the mean of these measurements was recorded. Height SDS CA Yx = (height Yx – reference mean for CA Yx) / reference SD for CA Yx; Yx refers to the value at particular timepoint x. Height in SDS was calculated using Sempe reference means and SD for height. CA calculated as integer (Date of height measurement–Date of birth)/365.25*12. PP analysis set included all subjects (excluding a site with GCP issues) who received at least 1 dose of GH, had at least 1 subsequent rating of height, no major protocol violation till first 3 years post initiation of treatment and total GH treatment duration of 36 months or more. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Primary

End point timeframe:

Baseline, Month 36

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: Statistical analysis has been provided in the attachment.

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n=21)	-2.86 (± 0.89)			
Change at Month 36 (n=19)	0.81 (± 1.18)			

Attachments (see zip file)	Change in height SDS for CA: PP population/change in height

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Height

End point title	Mean Height

End point description:

The standing height measurements were performed using a wall mounted device (example Harpenden Stadiometer). The standing height of the subject was measured two times and the mean of these measurements was recorded. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: centimeters (cm)				
arithmetic mean (standard deviation)				
Baseline (n=58)	133.9 (± 15.7)			
Month 12 (n=50)	139.5 (± 16.8)			
Month 24 (n=41)	146 (± 16.4)			
Month 36 (n=30)	150.4 (± 16)			
Month 48 (n=14)	152.4 (± 16)			
Month 60 (n=9)	156 (± 11.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Height Standard Deviation Score (SDS) for Bone Age (BA)

End point title	Mean Height Standard Deviation Score (SDS) for Bone Age (BA)

End point description:

The standing height measurements were performed using a wall mounted device (example Harpenden Stadiometer). The standing height of the subject was measured two times and the mean of these measurements was recorded. Height SDS BA Yx = (height Yx – reference mean for BA Yx) / reference SD for BA Yx; Yx refers to the value at particular timepoint x. Height in SDS was calculated using Sempe reference means and SD for height. BA was estimated locally using an X-ray from the left wrist and hand. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n=51)	-0.29 (± 1.15)			
Month 12 (n=40)	-0.36 (± 1.52)			
Month 24 (n=29)	0.11 (± 1.36)			
Month 36 (n=24)	0.14 (± 1.48)			
Month 48 (n=13)	-0.26 (± 1.28)			
Month 60 (n=7)	-0.19 (± 1.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Growth Rate (AGR)

End point title	Annual Growth Rate (AGR)

End point description:

AGR at Yx was derived by subtracting AGR at baseline from Yx value. AGR was calculated each year and re scaled to 1 year if the interval between Yx and Y[x-1] was not 365 days, as long as a subject remained in the study. AGR at Yx was calculated using the previous height measurements (Y[x-1]) and height recorded at Yx (AGR Yx = [height Yx–height Y{x-1}] / ([date of Yx – date of Y{x-1}] /365.25). Yx refers to the value at particular timepoint x. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: cm/year				
arithmetic mean (standard deviation)				
Baseline (n=52)	3 (± 2)			
Month 12 (n=49)	6.7 (± 2.6)			
Month 24 (n=41)	6 (± 2.7)			
Month 36 (n=30)	5.9 (± 2.7)			
Month 48 (n=14)	4.8 (± 2.5)			
Month 60 (n=9)	4.9 (± 3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Rate (GR) Standard Deviation Score (SDS) for Bone Age (BA)

End point title	Growth Rate (GR) Standard Deviation Score (SDS) for Bone Age (BA)

End point description:

GR SDS BA Yx = (GR Yx – reference mean for BA Yx) / reference SD for BA Yx; Yx refers to the value at particular timepoint x. GR in SDS was calculated using Sempe reference means and SD for GR. BA was estimated locally using an X-ray from the left wrist and hand. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of
height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: SDS				
arithmetic mean (standard deviation)				
Month 12 (n=36)	-0.13 (± 2.15)			
Month 24 (n=25)	0.07 (± 2.51)			
Month 36 (n=20)	0.05 (± 1.94)			
Month 48 (n=11)	-1 (± 1.38)			
Month 60 (n=7)	-0.43 (± 1.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Rate (GR) Standard Deviation Score (SDS) for Chronological Age (CA)

End point title	Growth Rate (GR) Standard Deviation Score (SDS) for Chronological Age (CA)

End point description:

GR SDS CA Yx = (GR Yx – reference mean for CA Yx) / reference SD for CA Yx; Yx refers to the value at particular timepoint x. GR in SDS was calculated using Sempe reference means and SD for GR. CA calculated as integer (Date of height measurement–Date of birth)/365.25*12. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n=52)	-2.04 (± 2.03)			
Month 12 (n=49)	1.77 (± 4.29)			
Month 24 (n=41)	5.26 (± 16.79)			
Month 36 (n=29)	3.64 (± 9.06)			
Month 48 (n=13)	0.93 (± 2.73)			
Month 60 (n=9)	1.4 (± 1.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Body Mass Index (BMI)

End point title	Body Mass Index (BMI)

End point description:

BMI was calculated by weight divided by height squared and measured as kilogram per square meter (kg/m^2). FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: kg/m^2				
arithmetic mean (standard deviation)				
Baseline (n=58)	19.4 (± 3.6)			
Month 12 (n=50)	19.1 (± 3.1)			
Month 24 (n=41)	19.4 (± 3)			
Month 36 (n=30)	19.4 (± 2.4)			
Month 48 (n=14)	19.7 (± 3)			
Month 60 (n=9)	20.8 (± 3.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height at Month 12, 24, 36, 48 and 60

End point title	Change From Baseline in Height at Month 12, 24, 36, 48 and 60

End point description:

The standing height measurements were performed using a wall mounted device (example Harpenden Stadiometer). The standing height of the subject was measured two times and the mean of these measurements was recorded. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n=58)	133.9 (± 15.7)			
Change at Month 12 (n=50)	6.8 (± 2.8)			
Change at Month 24 (n=41)	12.9 (± 4.7)			
Change at Month 36 (n=30)	18.8 (± 6.1)			
Change at Month 48 (n=14)	23.9 (± 8.5)			
Change at Month 60 (n=9)	30.3 (± 7.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height Standard Deviation Score (SDS) for Chronological Age (CA) at Month 12, 24, 48 and 60

End point title	Change From Baseline in Height Standard Deviation Score (SDS) for Chronological Age (CA) at Month 12, 24, 48 and 60

End point description:

The standing height measurements were performed using a wall mounted device (example Harpenden Stadiometer). The standing height of the subject was measured two times and the mean of these measurements was recorded. Height SDS CA Yx = (height Yx – reference mean for CA Yx) / reference SD for CA Yx; Yx refers to the value at particular timepoint x. Height in SDS was calculated using Sempe reference means and SD for height. CA calculated as integer (Date of height measurement–Date of birth)/365.25*12. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n=58)	-2.91 (± 1.19)			
Change at Month 12 (n=50)	0.28 (± 0.57)			
Change at Month 24 (n=41)	0.57 (± 0.95)			
Change at Month 48 (n=14)	0.82 (± 1.42)			
Change at Month 60 (n=9)	0.75 (± 1.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height Standard Deviation Score (SDS) for Bone Age (BA) at Month 12, 24, 36, 48 and 60

End point title	Change From Baseline in Height Standard Deviation Score (SDS) for Bone Age (BA) at Month 12, 24, 36, 48 and 60

End point description:

The standing height measurements were performed using a wall mounted device (example Harpenden Stadiometer). The standing height of the subject was measured two times and the mean of these measurements was recorded. Height SDS BA Yx = (height Yx – reference mean for BA Yx) / reference SD for BA Yx; Yx refers to the value at particular timepoint x. Height in SDS was calculated using Sempe reference means and SD for height. BA was estimated locally using an X-ray from the left wrist and hand. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n=51)	-0.29 (± 1.15)			
Change at Month 12 (n=36)	-0.02 (± 0.99)			
Change at Month 24 (n=26)	0.28 (± 1.18)			
Change at Month 36 (n=21)	0.31 (± 1.17)			
Change at Month 48 (n=13)	-0.08 (± 1.3)			
Change at Month 60 (n=7)	0.01 (± 1.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Age (BA) at Month 12, 24, 36, 48 and 60

End point title	Change From Baseline in Bone Age (BA) at Month 12, 24, 36, 48 and 60

End point description:

BA was estimated locally using an X-ray from the left wrist and hand. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: months				
arithmetic mean (standard deviation)				
Baseline (n=58)	117.9 (± 34.6)			
Change at Month 12 (n=37)	17.8 (± 11)			
Change at Month 24 (n=32)	28.2 (± 17.9)			
Change at Month 36 (n=23)	36.5 (± 17.8)			
Change at Month 48 (n=13)	52.8 (± 21.2)			
Change at Month 60 (n=7)	70 (± 27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of Bone Age (BA) to Chronological Age (CA)

End point title	Ratio of Bone Age (BA) to Chronological Age (CA)

End point description:

BA was estimated locally using an X-ray from the left wrist and hand. CA at the date of corresponding X-ray (Date of X-ray – Date of birth)/365.25. Ratio of BA/CA at each annual study visit was calculated. FAS included all subjects (excluding a site with GCP issues) who had received at least 1 injection of GH and had at least 1 post-Baseline measurement of height. Here "n" signifies those subjects who were evaluable for the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=58)	0.78 (± 0.1)			
Month 12 (n=37)	0.82 (± 0.11)			
Month 24 (n=32)	0.8 (± 0.09)			
Month 36 (n=23)	0.79 (± 0.1)			
Month 48 (n=13)	0.81 (± 0.08)			
Month 60 (n=7)	0.85 (± 0.1)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pretreatment state. AEs include both SAEs and non-SAEs. Safety analysis set included all subjects (including a site with GCP issues) who had received at least 1 study dose of GH.

End point type	Other pre-specified

End point timeframe:

Baseline up to 28 days after last study treatment

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: subjects				
AEs	84			
SAEs	45			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Significant Changes in Physical Examinations

End point title	Number of Subjects With Significant Changes in Physical Examinations

End point description:

Number of subjects with clinically significant physical examinations changes since previous visit were reported. Physical examination including estimation of pubertal stage and blood pressure measurement. Safety analysis set included all subjects (including a site with GCP issues) who had received at least 1 study dose of GH.

End point type	Other pre-specified

End point timeframe:

Baseline, Month 12, 24, 36, 48, 60, End of Treatment (EOT)

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: subjects				
Baseline (n=93)	1			
Month 12 (n=93)	16			
Month 24 (n=72)	16			
Month 36 (n=52)	5			
Month 48 (n=23)	4			
Month 60 (n=12)	2			
EOT (n=44)	11			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With at Least 1 Medical or Surgical History

End point title	Number of Subjects With at Least 1 Medical or Surgical History

End point description:

Safety analysis set included all subjects (including a site with GCP issues) who had received at least 1 study dose of GH.

End point type	Other pre-specified

End point timeframe:

Screening

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: subjects	67			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects Who Received Concomitant Medications

End point title	Number of Subjects Who Received Concomitant Medications

End point description:

Safety analysis set included all subjects (including a site with GCP issues) who had received at least 1 study dose of GH.

End point type	Other pre-specified

End point timeframe:

Baseline up to Month 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: subjects	98			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Fasting Serum Insulin Like Growth Factor-1 (IGF-1) Levels

End point title	Fasting Serum Insulin Like Growth Factor-1 (IGF-1) Levels

End point description:

Safety analysis set included all subjects (including a site with GCP issues) who had received at least 1 study dose of GH.

End point type	Other pre-specified

End point timeframe:

Screening, Month 6, 12, 18, 24, 30, 36, 42, 48, 54, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Screening (n=93)	335 (± 157)			
Month 6 (n=63)	604 (± 291)			
Month 12 (n=71)	538 (± 268)			
Month 18 (n=47)	624 (± 251)			
Month 24 (n=62)	579 (± 262)			
Month 30 (n=50)	559 (± 250)			
Month 36 (n=44)	511 (± 186)			
Month 42 (n=22)	555 (± 224)			
Month 48 (n=21)	581 (± 244)			
Month 54 (n=16)	593 (± 184)			
Month 60 (n=10)	501 (± 180)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Fasting and Postprandial Plasma Glucose Levels at Month 12,

24, 36, 48 and 60

End point title	Fasting and Postprandial Plasma Glucose Levels at Month 12, 24, 36, 48 and 60

End point description:

Fasting and 2 hours plasma glucose levels were assessed using standard oral glucose tolerance test (OGTT). Safety analysis set included all subjects (including a site with GCP issues) who had received at least 1 study dose of GH.

End point type	Other pre-specified

End point timeframe:

Screening, Month 12, 24, 36, 48, 60

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: milli mole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Glucose Fasting: Screening (n=91)	4.5 (± 0.7)			
Glucose Fasting: Month 12 (n=69)	4.6 (± 0.7)			
Glucose Fasting: Month 24 (n=59)	4.7 (± 0.6)			
Glucose Fasting: Month 36 (n=45)	4.6 (± 0.5)			
Glucose Fasting: Month 48 (n=20)	4.7 (± 0.4)			
Glucose Fasting: Month 60 (n=14)	4.5 (± 0.6)			
Glucose Postprandial: Screening (n=94)	5.6 (± 1.2)			
Glucose Postprandial: Month 12 (n=66)	6.1 (± 1.4)			
Glucose Postprandial: Month 24 (n=59)	6.1 (± 1.4)			
Glucose Postprandial: Month 36 (n=41)	6.4 (± 1.6)			
Glucose Postprandial: Month 48 (n=19)	6.1 (± 1.1)			
Glucose Postprandial: Month 60 (n=13)	6.3 (± 1.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline till 28 days after last study treatment

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and non serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Genotonorm

Reporting group description:

Subjects received genotonorm administered weekly, divided into 7 daily subcutaneous injections for up to 60 months.

Serious adverse events	Genotonorm		
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 98 (45.92%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Intermittent claudication			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral coldness			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrostomy closure			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee arthroplasty			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic operation			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth extraction			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		

Asthenia				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion site extravasation				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Graft versus host disease				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Social circumstances				
Treatment noncompliance				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Polycystic ovaries				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				

subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
accident			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Alcohol poisoning			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardiac failure				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Subvalvular aortic stenosis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Headache				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Benign intracranial hypertension				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral venous thrombosis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial pressure increased				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Optic neuritis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope vasovagal				

subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Histiocytosis haematophagic			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombotic microangiopathy			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visual acuity reduced			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Diarrhoea				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Aphthous stomatitis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Protein-losing gastroenteropathy				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal stenosis				

subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Varices oesophageal			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cytolytic hepatitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxic skin eruption			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	7 / 98 (7.14%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		

Renal failure			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epiphysiolysis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint destruction			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Knee deformity			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteochondrosis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Synovitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Systemic lupus erythematosus				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Gastroenteritis				
subjects affected / exposed	8 / 98 (8.16%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Empedobacter brevis infection				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis cryptosporidial				

subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis rotavirus				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nail bed infection				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periorbital cellulitis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pertussis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				

subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Genotonorm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 98 (82.65%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences (all)	4		
Acrochordon			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Skin papilloma			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences (all)	4		
Thrombosis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	8 / 98 (8.16%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	7 / 98 (7.14%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Vasculitis			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences (all)	8		
Epistaxis			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Lung disorder			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Pharyngeal erythema			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	3		
Rhinitis allergic			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Adenoidal hypertrophy			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Rhinorrhoea			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Affective disorder			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Investigations			
Insulin-like growth factor increased			
subjects affected / exposed	13 / 98 (13.27%)		
occurrences (all)	19		
Weight decreased			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Graft dysfunction			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Joint sprain			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Spinal compression fracture			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 98 (8.16%)		
occurrences (all)	15		
Dizziness			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	2		
Hemicephalalgia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Hyperreflexia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Hypotonia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Migraine			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Lymphadenopathy			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	3		
Anaemia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	2		
Anaemia of chronic disease			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Lymphadenitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	3		
Eye disorders			

Cataract				
subjects affected / exposed	4 / 98 (4.08%)			
occurrences (all)	4			
Conjunctivitis				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences (all)	4			
Ocular hypertension				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences (all)	3			
Papilloedema				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	2			
Uveitis				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	3			
Chalazion				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Eye disorder				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Myopia				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Night blindness				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Periorbital disorder				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	2			
Retinal detachment				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Visual acuity reduced				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			

Visual impairment			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Vitritis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 98 (9.18%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Gastritis			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Duodenitis			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Gingivitis			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Odynophagia			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Diarrhoea haemorrhagic			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Gingival hypertrophy			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Ileus			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Intestinal polyp			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Oral disorder			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cytolytic hepatitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences (all)	7		
Skin lesion			

subjects affected / exposed	5 / 98 (5.10%)			
occurrences (all)	5			
Rash				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences (all)	3			
Skin striae				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences (all)	3			
Dermatomyositis				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	3			
Acanthosis nigricans				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Alopecia				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Cutaneous lupus erythematosus				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Dermal cyst				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	2			
Ecchymosis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Eczema				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Erythema				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Hypertrichosis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Ingrowing nail				

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Pityriasis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Scar			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Skin hyperpigmentation			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Skin nodule			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	2		
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	11 / 98 (11.22%)		
occurrences (all)	37		
Dysuria			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Proteinuria			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	6		
Enuresis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Renal impairment			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		

Endocrine disorders			
Cushingoid			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 98 (9.18%)		
occurrences (all)	9		
Back pain			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences (all)	5		
Juvenile arthritis			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Scoliosis			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Arthritis			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	4		
Knee deformity			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Amyotrophy			

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Joint effusion			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	2		
Mobility decreased			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Rheumatoid arthritis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	3		
Tendonitis			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 98 (8.16%)		
occurrences (all)	13		
Nasopharyngitis			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences (all)	6		
Tonsillitis			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences (all)	6		
Gastroenteritis			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences (all)	5		

Pharyngitis				
subjects affected / exposed	5 / 98 (5.10%)			
occurrences (all)	5			
Influenza				
subjects affected / exposed	4 / 98 (4.08%)			
occurrences (all)	5			
Rhinitis				
subjects affected / exposed	4 / 98 (4.08%)			
occurrences (all)	4			
Varicella				
subjects affected / exposed	4 / 98 (4.08%)			
occurrences (all)	4			
Ear infection				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences (all)	4			
Urinary tract infection				
subjects affected / exposed	3 / 98 (3.06%)			
occurrences (all)	6			
Otitis media				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	3			
Respiratory tract infection				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	2			
Sinusitis				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	2			
Tinea pedis				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	2			
Upper respiratory tract infection				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	2			
Viral infection				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	2			

Chikungunya virus infection				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Cystitis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Dermatophytosis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Eye infection toxoplasmal				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Fungal skin infection				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Gangrene				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Impetigo				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Oral fungal infection				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Penile infection				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Pneumonia mycoplasmal				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Pyelonephritis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	2			

Tinea versicolour				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Tooth abscess				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Tooth infection				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Tracheitis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Trichophytosis				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Abdominal pain				
subjects affected / exposed	6 / 98 (6.12%)			
occurrences (all)	6			
Metabolism and nutrition disorders				
Glucose tolerance impaired				
subjects affected / exposed	8 / 98 (8.16%)			
occurrences (all)	8			
Anorexia				
subjects affected / exposed	2 / 98 (2.04%)			
occurrences (all)	2			
Diabetes mellitus				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Hyperglycaemia				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Hypertriglyceridaemia				
subjects affected / exposed	1 / 98 (1.02%)			
occurrences (all)	1			
Hypoglycaemia				

subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Obesity			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2005	1) Extended BA at the inclusion to less than (<) 15 years for males and <13 years for females. 2) Subjects treated with glucocorticoids at a dose lower than 0.2 mg/kg/day were also included.
13 November 2008	1) Inclusion period was extended 18 December 2009 in the study. 2) Duration of Genotonorm treatment was extended up to 5 years.
16 February 2011	1) The maximal tolerated dose of the genotonorm was specified to be limited to 50 mcg/kg/day.
14 August 2012	1) Inclusion criteria was changed to include obtaining agreement of subjects of childbearing potential to use a highly effective method of contraception throughout the study and for 28 days after the last dose of assigned treatment.

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.

One site in this study was found to have GCP related issues and was discontinued. Consequently, the Sponsor determined that the data from this site would be excluded from all efficacy analyses. For analysis of safety data, all sites were included.

Notes: