



Clinical trial results:

A Two Years Multicentre Study of Genotropin Treatment of Short Prepubertal Children With Intra-Uterine Growth Retardation

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-004160-38 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 07 May 2009 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 13 April 2016 |
| First version publication date | 27 June 2015 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | 93-8122-001 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01073605 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Alias: A6281186 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, 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 | 18 January 2010 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 May 2009 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of continuous and intermittent administration of Genotropin 16 international unit (IU) on stature in prepubertal short children with intra-uterine growth retardation (IUGR).

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 | 01 July 1993 |
| 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: 206 |
| Worldwide total number of subjects | 206 |
| EEA total number of subjects | 206 |

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) | 205 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 208 subjects were enrolled from 32 sites in France. Study started on 01 July 1993 and completed on 07 May 2009. Out of 208 enrolled subjects, only 206 subjects were treated.

Period 1

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

Arms

| | |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Genotonorm 0.7 (Continuous Treatment) |

Arm description:

Subjects received 0.7 IU/kilogram (kg)/week of Genotonorm growth hormone (GH) as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Genotonorm |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received 0.7 IU/kg/week at a dose of 0.03 milligram (mg)/kg/day of Genotonorm growth hormone (GH) as a continuous treatment.

| | |
|------------------|---------------------------------------|
| Arm title | Genotonorm 1.4 (Continuous Treatment) |
|------------------|---------------------------------------|

Arm description:

Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Genotonorm |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received 1.4 IU/kg/week at a dose of 0.06 mg/kg/day of growth hormone Genotonorm as a continuous treatment.

| | |
|------------------|---|
| Arm title | Genotonorm 1.4 (Intermittent Treatment) |
|------------------|---|

Arm description:

Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|------------------|
| Investigational medicinal product name | Genotonorm |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received 1.4 IU/kg/week at a dose of 0.06 mg/kg/day of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached.

| Number of subjects in period 1 | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) |
|---------------------------------------|--|--|--|
| Started | 68 | 70 | 68 |
| Received Treatment | 68 | 70 | 68 |
| Completed | 6 | 4 | 8 |
| Not completed | 62 | 66 | 60 |
| Consent withdrawn by subject | 31 | 39 | 22 |
| Unknown | 25 | 21 | 29 |
| Ongoing at Cutoff Date | 1 | 1 | - |
| Adverse event | 2 | 1 | - |
| Lost to follow-up | 3 | 4 | 9 |

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Genotonorm 0.7 (Continuous Treatment) |
| Reporting group description: Subjects received 0.7 IU/kilogram (kg)/week of Genotonorm growth hormone (GH) as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached. | |
| Reporting group title | Genotonorm 1.4 (Continuous Treatment) |
| Reporting group description: Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached. | |
| Reporting group title | Genotonorm 1.4 (Intermittent Treatment) |
| Reporting group description: Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached. | |

| Reporting group values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) |
|--|--|--|--|
| Number of subjects | 68 | 70 | 68 |
| Age, Customized | | | |
| Units: subjects | | | |
| Less than (<) 4 years | 15 | 8 | 6 |
| 4 - 8 years | 29 | 32 | 29 |
| 8 - 12 years | 23 | 30 | 33 |
| Greater than or equal to (>=) 12 years | 1 | 0 | 0 |
| Gender, Male/Female | | | |
| Units: subjects | | | |
| Female | 25 | 31 | 39 |
| Male | 43 | 39 | 29 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 206 | | |
| Age, Customized | | | |
| Units: subjects | | | |
| Less than (<) 4 years | 29 | | |
| 4 - 8 years | 90 | | |
| 8 - 12 years | 86 | | |
| Greater than or equal to (>=) 12 years | 1 | | |
| Gender, Male/Female | | | |
| Units: subjects | | | |
| Female | 95 | | |
| Male | 111 | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Genotonorm 0.7 (Continuous Treatment) |
| Reporting group description: Subjects received 0.7 IU/kilogram (kg)/week of Genotonorm growth hormone (GH) as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached. | |
| Reporting group title | Genotonorm 1.4 (Continuous Treatment) |
| Reporting group description: Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached. | |
| Reporting group title | Genotonorm 1.4 (Intermittent Treatment) |
| Reporting group description: Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached. | |

Primary: Change from Baseline in Annual Growth Rate Measured at 2 Years Following Treatment With Genotonorm

| | |
|--|--|
| End point title | Change from Baseline in Annual Growth Rate Measured at 2 Years Following Treatment With Genotonorm |
| End point description: Annual growth rate was expressed as height velocity (centimeter [cm]/year). This was derived by subtracting annual growth rate at Baseline from 2-year value. (Annual growth rate was calculated each year and rescaled to 1 year if the interval between x and x-1 was not 365 days, as long as a subject remains in the study): $ANGRY_x = (\text{Height } Y_x - \text{Height } Y_{[x-1]}) / ([\text{Date of } Y_x - \text{Date of } Y_{[x-1]}] / 365.25)$. All subjects who received at least 1 study dose of Genotonorm were included in the Full Analysis Set (FAS). | |
| End point type | Primary |
| End point timeframe: Baseline, 2 years | |

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|---------------------------------------|---------------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 47 ^[1] | 37 ^[2] | 40 ^[3] | |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | 3.07 (± 2.21) | 3.97 (± 1.72) | 2.84 (± 1.71) | |

Notes:

[1] - N signifies number of subjects with change in annual growth rate at 2 years.

[2] - N signifies number of subjects with change in annual growth rate at 2 years.

[3] - N signifies number of subjects with change in annual growth rate at 2 years.

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Genotonorm 0.7 vs. 1.4 (Continuous Treatment) |
| Comparison groups | Genotonorm 1.4 (Continuous Treatment) v Genotonorm 0.7 (Continuous Treatment) |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02922 ^[4] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[4] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|---|---|
| Statistical analysis title | Genotonorm 0.7 (Continuous) vs 1.4 (Intermittent) |
| Comparison groups | Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment) |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.74299 ^[5] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[5] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|---|---|
| Statistical analysis title | Genotonorm 1.4 (Continuous vs. Intermittent) |
| Comparison groups | Genotonorm 1.4 (Continuous Treatment) v Genotonorm 1.4 (Intermittent Treatment) |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.00467 ^[6] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[6] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Secondary: Annual Growth Rate Standard Deviation Score (SDS)

| | |
|-----------------|---|
| End point title | Annual Growth Rate Standard Deviation Score (SDS) |
|-----------------|---|

End point description:

Calculated using Sempe reference means and standard deviations for growth rate according to age and sex. Standardization was performed for chronological age. FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 1 to 6 years

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|-----------------------------|---------------------------------------|---------------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 50 ^[7] | 42 ^[8] | 43 ^[9] | |
| Units: SDS | | | | |

| arithmetic mean (standard deviation) | | | | |
|--------------------------------------|----------------|----------------|----------------|--|
| Baseline (n=50, 42, 43) | -2.72 (± 1.83) | -2.58 (± 1.39) | -2.75 (± 1.73) | |
| 1 year (n=57, 55, 59) | 2.14 (± 1.52) | 3.97 (± 2.26) | 1.71 (± 1.51) | |
| 2 years (n=53, 49, 56) | 0.77 (± 1.57) | 2 (± 1.73) | 0.67 (± 1.22) | |
| 3 years (n=39, 34, 41) | 0.36 (± 1.14) | 1.35 (± 1.78) | 0.31 (± 1.12) | |
| 4 years (n=21, 18, 27) | 0.13 (± 1.55) | 0.61 (± 1.2) | 0.34 (± 1.2) | |
| 5 years (n=12, 10, 20) | 0.18 (± 1.24) | 0.09 (± 0.88) | -0.02 (± 1.46) | |
| 6 years (n=11, 7, 19) | 0.9 (± 1.92) | 0.59 (± 1.61) | 0.05 (± 1.2) | |

Notes:

[7] - N signifies number of subjects with evaluable data at Baseline.

[8] - N signifies number of subjects with evaluable data at Baseline.

[9] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Annual Growth Rate SDS

| End point title | Change From Baseline in Annual Growth Rate SDS |
|--|--|
| End point description: | |
| Calculated corresponding to the gender and chronological age by subtracting annual growth rate SDS at baseline from annual growth rate SDS at each year. FAS. Here, n = number of subjects with evaluable data at each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 1 to 3 years | |

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 ^[10] | 42 ^[11] | 42 ^[12] | |
| Units: SDS | | | | |
| arithmetic mean (standard deviation) | | | | |
| 1 year (n=49, 42, 42) | 4.81 (± 2.27) | 6.56 (± 2.55) | 4.37 (± 2.16) | |
| 2 years (n=47, 37, 40) | 3.51 (± 2.5) | 4.53 (± 1.89) | 3.37 (± 2.33) | |
| 3 years (n=34, 25, 32) | 3.31 (± 2.06) | 3.8 (± 2.2) | 3.17 (± 1.86) | |

Notes:

[10] - N signifies number of subjects with evaluable data at 1 year.

[11] - N signifies number of subjects with evaluable data at 1 year.

[12] - N signifies number of subjects with evaluable data at 1 year.

Statistical analyses

| Statistical analysis title | Genotonorm 0.7 vs. 1.4 (Continuous Treatment) |
|-----------------------------------|---|
| Statistical analysis description: | |
| Statistical analysis for 1 year. | |
| Comparison groups | Genotonorm 1.4 (Continuous Treatment) v Genotonorm 0.7 (Continuous Treatment) |

| | |
|---|---------------------------|
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.00125 ^[13] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[13] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|-----------------------------------|--|
| Statistical analysis title | Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent) |
|-----------------------------------|--|

Statistical analysis description:

Statistical analysis for 1 year.

| | |
|---|---|
| Comparison groups | Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment) |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.25995 ^[14] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[14] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|-----------------------------------|--|
| Statistical analysis title | Genotonorm 1.4 (Continuous vs. Interimittent) Groups |
|-----------------------------------|--|

Statistical analysis description:

Statistical analysis for 1 year.

| | |
|---|---|
| Comparison groups | Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 1.4 (Continuous Treatment) |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.00008 ^[15] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[15] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|-----------------------------------|---|
| Statistical analysis title | Genotonorm 0.7 vs. 1.4 (Continuous Treatment) |
|-----------------------------------|---|

Statistical analysis description:

Statistical analysis for 2 years.

| | |
|---|---|
| Comparison groups | Genotonorm 0.7 (Continuous Treatment) v Genotonorm 1.4 (Continuous Treatment) |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.03273 ^[16] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[16] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|-----------------------------------|--|
| Statistical analysis title | Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent) |
|-----------------------------------|--|

Statistical analysis description:

Statistical analysis for 2 years.

| | |
|---|---|
| Comparison groups | Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment) |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.68581 ^[17] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[17] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|--|---|
| Statistical analysis title | Genotonorm 1.4 (Continuous vs. Intermittent) Groups |
| Statistical analysis description: Statistical analysis for 2 years. | |
| Comparison groups | Genotonorm 1.4 (Continuous Treatment) v Genotonorm 1.4 (Intermittent Treatment) |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0053 ^[18] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[18] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|--|---|
| Statistical analysis title | Genotonorm 0.7 vs. 1.4 (Continuous Treatment) |
| Statistical analysis description: Statistical analysis for 3 years. | |
| Comparison groups | Genotonorm 1.4 (Continuous Treatment) v Genotonorm 0.7 (Continuous Treatment) |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.57556 ^[19] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[19] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|--|---|
| Statistical analysis title | Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent) |
| Statistical analysis description: Statistical analysis for 3 years. | |
| Comparison groups | Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment) |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.63956 ^[20] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[20] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|-----------------------------------|---|
| Statistical analysis title | Genotonorm 1.4 (Continuous vs. Intermittent) Groups |
|-----------------------------------|---|

Statistical analysis description:

Statistical analysis for 3 years.

| | |
|---|---|
| Comparison groups | Genotonorm 1.4 (Continuous Treatment) v Genotonorm 1.4 (Intermittent Treatment) |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.16421 ^[21] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[21] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Secondary: Height (cm)

| | |
|-----------------|-------------|
| End point title | Height (cm) |
|-----------------|-------------|

End point description:

Performed by use of a wallmounted device (eg, Harpenden Stadiometer). Each subject was measured 3 times and the mean of these measurements was recorded as the present height. Final Height: Childrens were defined as reaching their final height when annual Growth Rate was less than 2 cm in the previous year and bone age was equal to or greater than 17 years in boys and equal to or greater than 15 years in girls. FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 1 to 6 years, final height

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|---------------------------------------|---------------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 ^[22] | 56 ^[23] | 60 ^[24] | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=58, 56, 60) | 105.22 (± 15.04) | 107.06 (± 12.29) | 106.44 (± 12.04) | |
| 1 year (n=57, 55, 59) | 113.38 (± 15.09) | 116.31 (± 12.24) | 113.71 (± 12.01) | |
| 2 years (n=53, 49, 56) | 119.67 (± 15.18) | 124.11 (± 13.02) | 120.64 (± 12.34) | |
| 3 years (n=39, 34, 41) | 123.92 (± 15.08) | 131.75 (± 13.76) | 125.39 (± 12.52) | |
| 4 years (n=21, 18, 27) | 124.67 (± 13.14) | 132.3 (± 13.23) | 127.59 (± 11.51) | |
| 5 years (n=12, 10, 21) | 126.73 (± 10.01) | 131.01 (± 9.26) | 129.98 (± 9.93) | |
| 6 years (n=11, 7, 20) | 133.29 (± 10.46) | 138.84 (± 8.69) | 135.45 (± 10.1) | |
| Final height (n=17, 12, 22) | 146.86 (± 11.26) | 151.98 (± 6.52) | 149.13 (± 9.07) | |

Notes:

[22] - N signifies number of subjects with evaluable data at Baseline.

[23] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height (cm)

| | |
|-----------------|-------------------------------------|
| End point title | Change From Baseline in Height (cm) |
|-----------------|-------------------------------------|

End point description:

Calculated by subtracting height at Baseline from height at each year. Final Height: Children were defined as reaching their final height when annual Growth Rate was less than 2 cm in the previous year and bone age was equal to or greater than 17 years in boys and equal to or greater than 15 years in girls. FAS. Here, n = number of subjects with evaluable data at Baseline and each time point. Data beyond 6 years were not reported due to the low proportion of subjects followed up beyond 6 years.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 1 to 6 years, final height

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 ^[25] | 56 ^[26] | 60 ^[27] | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| 1 year (n=57, 55, 59) | 8.21 (± 1.38) | 9.21 (± 1.45) | 7.33 (± 1.32) | |
| 2 years (n=53, 49, 56) | 14.77 (± 2.45) | 17.01 (± 2.21) | 13.92 (± 2.03) | |
| 3 years (n=39, 34, 41) | 20.62 (± 3) | 24.49 (± 3.04) | 20.14 (± 2.78) | |
| 4 years (n=21, 18, 27) | 26.36 (± 4.37) | 30.77 (± 3.43) | 25.83 (± 3.26) | |
| 5 years (n=12, 10, 21) | 32.23 (± 5.92) | 35.7 (± 4.27) | 32.16 (± 3.81) | |
| 6 years (n=11, 7, 20) | 38.2 (± 6.66) | 44.03 (± 3.09) | 38.01 (± 4.82) | |
| Final height (n=17, 12, 22) | 45.39 (± 13.08) | 45.3 (± 13.72) | 40.93 (± 9.22) | |

Notes:

[25] - N signifies number of subjects with evaluable data at Baseline.

[26] - N signifies number of subjects with evaluable data at Baseline.

[27] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Height (SDS)

| | |
|-----------------|--------------|
| End point title | Height (SDS) |
|-----------------|--------------|

End point description:

Calculated using Sempe reference means and standard deviations for height. Final Height: Children were

defined as reaching their final height when annual Growth Rate was less than 2 cm in the previous year and bone age was equal to or greater than 17 years in boys and equal to or greater than 15 years in girls. FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years were not reported due to the low proportion of subjects followed up beyond 6 years.

| | |
|--------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 1 to 6 years, final height | |

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 ^[28] | 56 ^[29] | 60 ^[30] | |
| Units: SDS | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=58, 56, 60) | -3.16 (± 0.52) | -3.07 (± 0.46) | -3.21 (± 0.65) | |
| 1 year (n=57, 55, 59) | -2.49 (± 0.54) | -2.17 (± 0.5) | -2.68 (± 0.69) | |
| 2 years (n=53, 49, 56) | -2.21 (± 0.66) | -1.68 (± 0.52) | -2.38 (± 0.75) | |
| 3 years (n=39, 34, 41) | -2.17 (± 0.7) | -1.38 (± 0.57) | -2.24 (± 0.9) | |
| 4 years (n=21, 18, 27) | -2.16 (± 1.03) | -1.16 (± 0.73) | -2.09 (± 0.96) | |
| 5 years (n=12, 10, 21) | -1.95 (± 1.26) | -1.15 (± 0.83) | -1.96 (± 1.1) | |
| 6 years (n=11, 7, 19) | -1.8 (± 1.28) | -0.67 (± 0.66) | -1.93 (± 1.18) | |
| Final height (n=14, 9, 18) | -2.06 (± 0.76) | -1.97 (± 0.95) | -2.29 (± 1.35) | |

Notes:

[28] - N signifies number of subjects with evaluable data at Baseline.

[29] - N signifies number of subjects with evaluable data at Baseline.

[30] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height (SDS)

| | |
|---|--------------------------------------|
| End point title | Change From Baseline in Height (SDS) |
| End point description: | |
| Calculated by subtracting height SDS at Baseline from height SDS at each year. Final Height: Children were defined as reaching their final height when annual Growth Rate was less than 2 cm in the previous year and bone age was equal to or greater than 17 years in boys and equal to or greater than 15 years in girls. FAS. Here, n = number of subjects with evaluable data at Baseline and each time point. Data beyond 6 years were not reported due to the low proportion of subjects followed up beyond 6 years. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 1 to 6 years, final height | |

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 ^[31] | 56 ^[32] | 60 ^[33] | |
| Units: SDS | | | | |
| arithmetic mean (standard deviation) | | | | |
| 1 year (n=57, 55, 59) | 0.67 (± 0.28) | 0.88 (± 0.3) | 0.53 (± 0.28) | |
| 2 years (n=53, 49, 56) | 0.94 (± 0.45) | 1.4 (± 0.43) | 0.84 (± 0.37) | |
| 3 years (n=39, 34, 41) | 1.06 (± 0.54) | 1.7 (± 0.54) | 0.99 (± 0.51) | |
| 4 years (n=21, 18, 27) | 1.2 (± 0.81) | 1.98 (± 0.69) | 1.21 (± 0.54) | |
| 5 years (n=12, 10, 21) | 1.37 (± 1.12) | 2.03 (± 0.87) | 1.46 (± 0.69) | |
| 6 years (n=11, 7, 19) | 1.54 (± 1.12) | 2.6 (± 0.66) | 1.54 (± 0.86) | |
| Final height (n=14, 9, 18) | 1 (± 0.53) | 0.97 (± 0.95) | 0.86 (± 1.16) | |

Notes:

[31] - N signifies number of subjects with evaluable data at Baseline.

[32] - N signifies number of subjects with evaluable data at Baseline.

[33] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Genotonorm 0.7 vs. 1.4 (Continuous Treatment) |
| Comparison groups | Genotonorm 0.7 (Continuous Treatment) v Genotonorm 1.4 (Continuous Treatment) |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 ^[34] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[34] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|---|---|
| Statistical analysis title | Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent) |
| Comparison groups | Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment) |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58324 ^[35] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[35] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

| | |
|-----------------------------------|---|
| Statistical analysis title | Genotonorm 1.4 (Continuous vs. Intermittent) Groups |
| Comparison groups | Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 1.4 (Continuous Treatment) |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[36] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[36] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Secondary: Body Mass Index (BMI)

| | |
|-----------------|-----------------------|
| End point title | Body Mass Index (BMI) |
|-----------------|-----------------------|

End point description:

BMI was calculated by weight divided by height squared. FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 1 to 6 years

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 ^[37] | 56 ^[38] | 60 ^[39] | |
| Units: kg/m ² | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=58, 56, 60) | 14.74 (± 1.48) | 15.14 (± 1.76) | 14.59 (± 1.51) | |
| 1 year (n=56, 55, 59) | 14.82 (± 1.52) | 15.44 (± 1.94) | 14.87 (± 1.76) | |
| 2 years (n=53, 49, 56) | 15.33 (± 1.78) | 15.92 (± 2.15) | 15.29 (± 2) | |
| 3 years (n=39, 34, 41) | 15.59 (± 2.02) | 16.65 (± 2.92) | 15.58 (± 2.11) | |
| 4 years (n=21, 18, 27) | 15.32 (± 1.56) | 17.03 (± 3.7) | 15.8 (± 2.37) | |
| 5 years (n=12, 10, 21) | 15.8 (± 1.57) | 16.25 (± 1.7) | 16.69 (± 3.92) | |
| 6 years (n=11, 7, 20) | 16.21 (± 1.46) | 16.34 (± 1.8) | 17.28 (± 4.21) | |

Notes:

[37] - N signifies number of subjects with evaluable data at Baseline.

[38] - N signifies number of subjects with evaluable data at Baseline.

[39] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Weight

| | |
|-----------------|--------|
| End point title | Weight |
|-----------------|--------|

End point description:

FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 1 to 6 years

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 ^[40] | 56 | 60 | |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=58, 56, 60) | 16.77 (± 5.43) | 17.7 (± 5.12) | 16.79 (± 4.35) | |
| 1 year (n=56, 55, 59) | 19.71 (± 6.28) | 21.29 (± 6.04) | 19.56 (± 5.17) | |
| 2 years (n=53, 49, 56) | 22.66 (± 7.62) | 25.08 (± 7.43) | 22.64 (± 6.05) | |
| 3 years (n=39, 34, 41) | 24.77 (± 8.8) | 29.61 (± 9.62) | 24.98 (± 7.05) | |
| 4 years (n=21, 18, 27) | 24.3 (± 7.01) | 30.56 (± 10.42) | 26.28 (± 7.94) | |
| 5 years (n=12, 10, 21) | 25.74 (± 6.22) | 28.07 (± 5.22) | 28.52 (± 8.96) | |
| 6 years (n=11, 7, 21) | 29.13 (± 6.42) | 31.94 (± 7.28) | 32.3 (± 10.32) | |

Notes:

[40] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Age

| | |
|--|----------------------------------|
| End point title | Change From Baseline in Bone Age |
| End point description: | |
| Bone age was determined by the Greulich-Pyle method. Calculated by subtracting bone age at baseline from bone age at each year. Safety population = all subjects who received at least 1 study dose of GH. Here, n = number of subjects with evaluable data at baseline and each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 1 to 3 years | |

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 ^[41] | 62 ^[42] | 61 ^[43] | |
| Units: Years | | | | |
| arithmetic mean (standard deviation) | | | | |
| 1 year (n=53, 60, 56) | 1.17 (± 0.51) | 1.27 (± 0.72) | 1.25 (± 0.54) | |
| 2 years (n=52, 51, 49) | 2.4 (± 0.9) | 2.5 (± 1.08) | 2.58 (± 0.97) | |
| 3 years (n=41, 39, 35) | 3.53 (± 1.22) | 4.06 (± 1.05) | 3.67 (± 0.97) | |

Notes:

[41] - N signifies number of subjects with evaluable data at Baseline.

[42] - N signifies number of subjects with evaluable data at Baseline.

[43] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Age/Change from Baseline in Chronological Age Ratio

| | |
|-----------------|--|
| End point title | Change From Baseline in Bone Age/Change from Baseline in Chronological Age Ratio |
|-----------------|--|

End point description:

Bone age was determined by the Greulich-Pyle method. Chronological Age (years) was calculated as: (Date minus Date of Birth) divided by 365.25. Chronological Age used was the age at the date that the corresponding Bone Age X-ray was performed. Ratio was calculated by change from Baseline in bone age divided by change from Baseline in chronological age. Safety population. Here, n = number of subjects with evaluable data at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 to 3 years

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 53 ^[44] | 60 ^[45] | 56 ^[46] | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| 1 year (n=53, 60, 56) | 0.96 (± 0.41) | 1.07 (± 0.62) | 1.06 (± 0.45) | |
| 2 years (n=51, 51, 49) | 1.06 (± 0.41) | 1.14 (± 0.5) | 1.18 (± 0.44) | |
| 3 years (n=35, 37, 35) | 1.09 (± 0.39) | 1.26 (± 0.32) | 1.14 (± 0.29) | |

Notes:

[44] - N signifies number of subjects with evaluable data at 1 year.

[45] - N signifies number of subjects with evaluable data at 1 year.

[46] - N signifies number of subjects with evaluable data at 1 year.

Statistical analyses

No statistical analyses for this end point

Secondary: Chronological Age at Onset of Puberty

| | |
|-----------------|---------------------------------------|
| End point title | Chronological Age at Onset of Puberty |
|-----------------|---------------------------------------|

End point description:

Chronological age (years) at first study visit with onset of puberty = (Date of study visit minus Date of Birth) divided by 365.25. Safety population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Onset of puberty

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 ^[47] | 35 ^[48] | 45 ^[49] | |
| Units: Years | | | | |
| arithmetic mean (standard deviation) | 11.88 (± 2.22) | 11.12 (± 1.74) | 11.58 (± 1.42) | |

Notes:

[47] - N signifies number of subjects who started puberty by the end of the study.

[48] - N signifies number of subjects who started puberty by the end of the study.

[49] - N signifies number of subjects who started puberty by the end of the study.

Statistical analyses

| Statistical analysis title | Genotonorm 0.7 vs. 1.4 (Continuous Treatment) |
|---|---|
| Comparison groups | Genotonorm 1.4 (Continuous Treatment) v Genotonorm 0.7 (Continuous Treatment) |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0681 ^[50] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 1.39 |

Notes:

[50] - There is no adjustment for multiplicity of treatment comparisons. The Analysis of Covariance took into account the patient covariates age and gender.

| Statistical analysis title | Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent) |
|---|---|
| Comparison groups | Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 1.4 (Continuous Treatment) |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8971 ^[51] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.05 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.65 |
| upper limit | 0.74 |

Notes:

[51] - There is no adjustment for multiplicity of treatment comparisons. The Analysis of Covariance took into account the patient covariates age and gender.

| | |
|---|---|
| Statistical analysis title | Genotonorm 1.4 (Continuous vs.Intermittent) Groups |
| Comparison groups | Genotonorm 1.4 (Continuous Treatment) v Genotonorm 1.4 (Intermittent Treatment) |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0583 ^[52] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.27 |
| upper limit | 0.02 |

Notes:

[52] - There is no adjustment for multiplicity of treatment comparisons. The Analysis of Covariance took into account the patient covariates age and gender.

Secondary: Number of Subjects Reaching Puberty

| | |
|---|-------------------------------------|
| End point title | Number of Subjects Reaching Puberty |
| End point description: | |
| The defined criteria for reaching puberty were: boy=if right or left testes volume >=4 ml; girl=if breast development >=2. Tanner Adolescent Pubertal Staging Questionnaire documents the stage of development of secondary sexual characteristics rated in 5 stages: stage 1 (no development) to 5 (adult-like development in quantity and size). Onset of puberty was defined as the visit where the data recorded first met the above criteria for starting puberty. Safety population. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years. Started = started puberty; Not Started = not started puberty yet as per Tanner scale. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 1 to 6 years | |

| End point values | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) | |
|--------------------------------|---------------------------------------|---------------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 70 | 68 | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| Baseline (Female, Not Started) | 25 | 31 | 39 | |
| Baseline (Male, Not Started) | 43 | 39 | 29 | |

| | | | | |
|-------------------------------|----|----|----|--|
| 1 year (Female, Not Started) | 24 | 27 | 37 | |
| 1 year (Female, Started) | 1 | 3 | 2 | |
| 1 year (Male, Not Started) | 36 | 35 | 27 | |
| 1 year (Male, Started) | 4 | 3 | 1 | |
| 2 years (Female, Not Started) | 20 | 20 | 31 | |
| 2 years (Female, Started) | 3 | 7 | 6 | |
| 2 years (Male, Not Started) | 31 | 28 | 20 | |
| 2 years (Male, Started) | 9 | 7 | 6 | |
| 3 years (Female, Not Started) | 16 | 10 | 16 | |
| 3 years (Female, Started) | 3 | 9 | 11 | |
| 3 years (Male, Not Started) | 19 | 15 | 9 | |
| 3 years (Male, Started) | 6 | 7 | 4 | |
| 4 years (Female, Not Started) | 10 | 7 | 10 | |
| 4 years (Female, Started) | 2 | 5 | 7 | |
| 4 years (Male, Not Started) | 10 | 5 | 7 | |
| 4 years (Male, Started) | 1 | 2 | 3 | |
| 5 years (Female, Not Started) | 5 | 4 | 5 | |
| 5 years (Female, Started) | 2 | 3 | 10 | |
| 5 years (Male, Not Started) | 6 | 6 | 4 | |
| 5 years (Male, Started) | 2 | 1 | 1 | |
| 6 years (Female, Not Started) | 3 | 3 | 3 | |
| 6 years (Female, Started) | 3 | 2 | 12 | |
| 6 years (Male, Not Started) | 5 | 4 | 1 | |
| 6 years (Male, Started) | 3 | 1 | 4 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were reported from time of first dose of study treatment up to 7 days after last dose of study treatment.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Genotonorm 0.7 (Continuous Treatment) |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received 0.7 IU/kg/week (0.03 milligram [mg]/kg/day) of Genotonorm growth hormone (GH) as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Genotonorm 1.4 (Continuous Treatment) |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received 1.4 IU/kg/week (0.06 mg/kg/day) of the growth hormone Genotonorm as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.

| | |
|-----------------------|---|
| Reporting group title | Genotonorm 1.4 (Intermittent Treatment) |
|-----------------------|---|

Reporting group description:

Subjects received 1.4 IU/kg/week (0.06 mg/kg/day) of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached.

| Serious adverse events | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 68 (8.82%) | 19 / 70 (27.14%) | 9 / 68 (13.24%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Appendicectomy | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hospitalisation | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mastoidectomy | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orchidopexy | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 0 / 70 (0.00%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthopaedic procedure | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngeal reconstruction | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 0 / 70 (0.00%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgery | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 3 / 70 (4.29%) | 4 / 68 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tenotomy | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tongue tie operation | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillectomy | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth extraction | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 68 (1.47%) | 0 / 70 (0.00%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour excision | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 0 / 70 (0.00%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric repair | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 2 / 70 (2.86%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Testicular disorder | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Testicular torsion | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 0 / 70 (0.00%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic fracture | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| DiGeorge's syndrome | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 0 / 70 (0.00%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Photophobia | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Visual acuity reduced | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 68 (1.47%) | 0 / 70 (0.00%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Anal prolapse | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 0 / 70 (0.00%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Precocious puberty | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nuchal rigidity | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteochondrosis | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 1 / 70 (1.43%) | 3 / 68 (4.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 70 (0.00%) | 1 / 68 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Genotonorm 0.7 (Continuous Treatment) | Genotonorm 1.4 (Continuous Treatment) | Genotonorm 1.4 (Intermittent Treatment) |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 68 (58.82%) | 42 / 70 (60.00%) | 35 / 68 (51.47%) |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 4 / 70 (5.71%) | 0 / 68 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 68 (2.94%) | 5 / 70 (7.14%) | 3 / 68 (4.41%) |
| occurrences (all) | 5 | 8 | 6 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 68 (5.88%) | 3 / 70 (4.29%) | 3 / 68 (4.41%) |
| occurrences (all) | 4 | 4 | 4 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 68 (5.88%) | 3 / 70 (4.29%) | 4 / 68 (5.88%) |
| occurrences (all) | 6 | 3 | 4 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 68 (7.35%) | 0 / 70 (0.00%) | 4 / 68 (5.88%) |
| occurrences (all) | 6 | 0 | 4 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 5 / 68 (7.35%) | 3 / 70 (4.29%) | 3 / 68 (4.41%) |
| occurrences (all) | 8 | 3 | 3 |
| Cough | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 3 / 70 (4.29%) | 5 / 68 (7.35%) |
| occurrences (all) | 1 | 3 | 6 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 4 / 68 (5.88%) | 1 / 70 (1.43%) | 1 / 68 (1.47%) |
| occurrences (all) | 9 | 1 | 1 |
| Urticaria | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 4 / 68 (5.88%) 6 | 0 / 70 (0.00%) 0 | 1 / 68 (1.47%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Scoliosis | | | |
| subjects affected / exposed | 2 / 68 (2.94%) | 4 / 70 (5.71%) | 0 / 68 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 13 / 68 (19.12%) | 9 / 70 (12.86%) | 17 / 68 (25.00%) |
| occurrences (all) | 20 | 18 | 32 |
| Ear infection | | | |
| subjects affected / exposed | 15 / 68 (22.06%) | 15 / 70 (21.43%) | 9 / 68 (13.24%) |
| occurrences (all) | 25 | 39 | 21 |
| Fungal infection | | | |
| subjects affected / exposed | 4 / 68 (5.88%) | 1 / 70 (1.43%) | 0 / 68 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 4 / 68 (5.88%) | 8 / 70 (11.43%) | 11 / 68 (16.18%) |
| occurrences (all) | 4 | 11 | 21 |
| Influenza | | | |
| subjects affected / exposed | 6 / 68 (8.82%) | 9 / 70 (12.86%) | 7 / 68 (10.29%) |
| occurrences (all) | 7 | 15 | 8 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 16 / 68 (23.53%) | 16 / 70 (22.86%) | 11 / 68 (16.18%) |
| occurrences (all) | 27 | 28 | 21 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 68 (2.94%) | 6 / 70 (8.57%) | 7 / 68 (10.29%) |
| occurrences (all) | 4 | 8 | 8 |
| Rhinitis | | | |
| subjects affected / exposed | 4 / 68 (5.88%) | 2 / 70 (2.86%) | 6 / 68 (8.82%) |
| occurrences (all) | 5 | 2 | 8 |
| Tracheitis | | | |
| subjects affected / exposed | 3 / 68 (4.41%) | 5 / 70 (7.14%) | 2 / 68 (2.94%) |
| occurrences (all) | 3 | 6 | 2 |
| Upper respiratory tract infection | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 19 / 68 (27.94%) | 19 / 70 (27.14%) | 12 / 68 (17.65%) |
| occurrences (all) | 31 | 39 | 20 |
| Varicella | | | |
| subjects affected / exposed | 8 / 68 (11.76%) | 6 / 70 (8.57%) | 1 / 68 (1.47%) |
| occurrences (all) | 8 | 6 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 18 December 1995 | Treatment with Genotonorm was stopped in prepubescent children with short stature due to IUGR who, after 2 years on the initial protocol or during their third year of treatment, had begun puberty at least 6 months before. The aim of this change was to study the spontaneous progress of their growth until reaching final height. |
| 15 June 1998 | Treatment of children with Genotonorm ® for one additional year was continued , in order to obtain long-term data on the safety and efficacy of the product, that subjects who started puberty would continue to be treated according to the same therapeutic regimen, for the possibility of using the Genotonorm ® Pen 16 or 36, depending on the weight of the subject and subjects who had discontinued their treatment were to be followed in the context of the protocol so as to obtain data on their final height. |
| 17 September 2001 | A modification of the treatment period was done, allowing the administration of Genotonorm to children until they attain their final height in order to obtain long-term data on the safety and efficacy of the product. Changes in dosage units of 5.3 mg instead of 16 IU and 12 mg instead of 36 IU. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported