



Clinical trial results:

Prevention of Retarded Growth by Early Treatment with Recombinant Human Growth Factor Genotonorm (Registered) in Children with Systemic Forms of Chronic Juvenile Arthritis Receiving Long-term Corticosteroid Therapy. Extension of the Study Beyond Three Years Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-004105-32 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 28 October 2011 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 13 April 2016 |
| First version publication date | 09 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | 307-MET-9002-052 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00174291 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Alias: A6281024 |

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., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer 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 | 06 November 2012 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 October 2011 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

-To evaluate the effect of increasing the Human growth hormone (hGH) dose (0.6 versus 0.46 milligram per kilogram per week [mg/kg/week] or 1.8 versus 1.4 international unit per kilogram per week [IU/kg/week]) on the statural response:

- 1) in subjects initially in the treated group of Study CTN 97-8129-016, by comparing the statural response observed with that obtained during the first therapeutic phase at a dose of 0.46 mg/kg/week, or 1.4 IU/kg/week.
- 2) in subjects initially in the control group of Study CTN 97-8129-016, by comparing the statural response observed with that of subjects in study CTN 94-8123-014.

-To assess the value of early treatment during the course of arthritic disease by comparing the height acquired in the medium term by subjects in the two dose groups: treated from the start or 1 year to 15 months after the diagnosis of Chronic Juvenile Arthritis (CJA), or treated for 4 years after the diagnosis.

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 | 26 March 2002 |
| 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: 21 |
| Worldwide total number of subjects | 21 |
| EEA total number of subjects | 21 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 18 |
| Adolescents (12-17 years) | 3 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects included in previous study CTN 97-8129-016 were eligible for this study.

Pre-assignment

Screening details:

This study was conducted in France from 26 March 2002 to 28 October 2011.

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 | Somatropin (Without Previous Somatropin Exposure) |
|------------------|---------------------------------------------------|

Arm description:

Subjects who received matching placebo for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 microgram/kilogram/day (mcg/kg/day), subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was less than or equal (\leq) 1.5 centimeter (cm) per year during the preceding 12 months and bone age was greater than or equal to (\geq) 17 years for boys and 15 years for girls.

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

Dosage and administration details:

Subjects received somatropin (Genotonorm) up to 0.6 mg/kg/week, equivalent to 1.8 IU/kg/week, divided in 7 daily doses subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, equivalent to 1.4 IU/kg/week, divided in 7 daily doses subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, equivalent to 0.35 mg/kg/week or 1.05 IU/kg/week, subcutaneously until the final height was reached or up to Year 8.5.

| | |
|------------------|------------------------------------------------|
| Arm title | Somatropin (With Previous Somatropin Exposure) |
|------------------|------------------------------------------------|

Arm description:

Subjects who received low dose of somatropin (Genotonorm) for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was \leq 1.5 cm per year during the preceding 12 months and bone age was \geq 17 years for boys and 15 years for girls.

| | |
|----------------------------------------|------------------|
| Arm type | Experimental |
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| Number of subjects in period 1 | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) |
|---------------------------------------|----------------------------------------------------------|-------------------------------------------------------|
| Started | 10 | 11 |
| Completed | 4 | 6 |
| Not completed | 6 | 5 |
| Consent withdrawn by subject | 3 | 3 |
| Study terminated by sponsor | - | 1 |
| Protocol Violation | 2 | - |
| Lost to follow-up | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------------------------------|
| Reporting group title | Somatropin (Without Previous Somatropin Exposure) |
|-----------------------|---------------------------------------------------|

Reporting group description:

Subjects who received matching placebo for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 microgram/kilogram/day (mcg/kg/day), subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was less than or equal (\leq) 1.5 centimeter (cm) per year during the preceding 12 months and bone age was greater than or equal to (\geq) 17 years for boys and 15 years for girls.

| | |
|-----------------------|------------------------------------------------|
| Reporting group title | Somatropin (With Previous Somatropin Exposure) |
|-----------------------|------------------------------------------------|

Reporting group description:

Subjects who received low dose of somatropin (Genotonorm) for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was ≤ 1.5 cm per year during the preceding 12 months and bone age was ≥ 17 years for boys and 15 years for girls.

| Reporting group values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | Total |
|------------------------------------|---------------------------------------------------|------------------------------------------------|-------|
| Number of subjects | 10 | 11 | 21 |
| Age categorical Units: Subjects | | | |

| | | | |
|-------------------------------------------------------------------------|------------------|------------------|----|
| Age Continuous Units: years arithmetic mean standard deviation | 8.5 ± 3.3 | 8.3 ± 2.6 | - |
| Gender, Male/Female Units: subjects | | | |
| Female | 4 | 6 | 10 |
| Male | 6 | 5 | 11 |

End points

End points reporting groups

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Reporting group title | Somatropin (Without Previous Somatropin Exposure) |
| Reporting group description: Subjects who received matching placebo for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 microgram/kilogram/day (mcg/kg/day), subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was less than or equal (\leq) 1.5 centimeter (cm) per year during the preceding 12 months and bone age was greater than or equal to (\geq) 17 years for boys and 15 years for girls. | |
| Reporting group title | Somatropin (With Previous Somatropin Exposure) |
| Reporting group description: Subjects who received low dose of somatropin (Genotonorm) for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was \leq 1.5 cm per year during the preceding 12 months and bone age was \geq 17 years for boys and 15 years for girls. | |

Primary: Change from Baseline in Annual Rate of Growth Standard Deviation Score (SDS) at Year 3

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Annual Rate of Growth Standard Deviation Score (SDS) at Year 3 ^[1] |
| End point description: Annual rate of growth SDS was obtained by measuring the annual growth rate, subtracting chronological age- and gender-appropriate mean annual growth rate and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. Full Analysis Set (FAS) included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. | |
| End point type | Primary |
| End point timeframe: Baseline, Year 3 | |

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: Only descriptive data was planned to be reported for this endpoint.

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------|------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 ^[2] | 6 ^[3] | | |
| Units: SDS | | | | |
| median (full range (min-max)) | | | | |
| Baseline | -2.96 (-6.4 to 1.5) | -0.21 (-3 to 4.5) | | |
| Change at Year 3 | 3.52 (-5.1 to 11.2) | 1.34 (-3.6 to 6.2) | | |

Notes:

[2] - Subjects who were evaluable for this measure.

[3] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Annual Rate of Growth Standard Deviation Score (SDS) at Final Height

| | |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Annual Rate of Growth Standard Deviation Score (SDS) at Final Height ^[4] |
|-----------------|-------------------------------------------------------------------------------------------------------------|

End point description:

Annual rate of growth SDS was obtained by measuring the annual growth rate, subtracting chronological age- and gender-appropriate mean annual growth rate and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, final height (assessed up to Year 9.5)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | | |
| Units: SDS | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[5] - Data was not analyzed because of change in planned analysis after early termination of the study.

[6] - Data was not analyzed because of change in planned analysis after early termination of the study.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Height Standard Deviation Score (SDS) at Year 3

| | |
|-----------------|----------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Height Standard Deviation Score (SDS) at Year 3 ^[7] |
|-----------------|----------------------------------------------------------------------------------------|

End point description:

Height was measured using a wall mounted device (example, Harpenden stadiometer). Height SDS was obtained by measuring the height, subtracting chronological age- and gender-appropriate mean height and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement.

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline, Year 3 | |
| Notes: | |
| [7] - 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: Only descriptive data was planned to be reported for this endpoint. | |

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 ^[8] | 6 ^[9] | | |
| Units: SDS | | | | |
| median (full range (min-max)) | | | | |
| Baseline | -2.34 (-4.8 to -1.4) | -0.61 (-3.7 to 1.4) | | |
| Change at Year 3 | 1.21 (-0.7 to 2.4) | 0.73 (-2.4 to 2.6) | | |

Notes:

[8] - Subjects who were evaluable for this measure.

[9] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Height Standard Deviation Score (SDS) at Final Height

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Height Standard Deviation Score (SDS) at Final Height ^[10] |
| End point description: | |
| Height was measured using a wall mounted device (example, Harpenden stadiometer). Height SDS was obtained by measuring the height, subtracting chronological age- and gender-appropriate mean height and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, final height (assessed up to Year 9.5) | |
| Notes: | |
| [10] - 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: Only descriptive data was planned to be reported for this endpoint. | |

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 ^[11] | 3 ^[12] | | |
| Units: SDS | | | | |
| median (full range (min-max)) | | | | |

| | | | | |
|------------------------|----------------------|---------------------|--|--|
| Baseline | -0.94 (-1.4 to -0.5) | 0.96 (-3.7 to 2.3) | | |
| Change at Final Height | 0.08 (-0.7 to 0.9) | -0.43 (-0.8 to 0.5) | | |

Notes:

[11] - Subjects who were evaluable for this measure.

[12] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Predicted Height Standard Deviation Score (SDS) at Year 3

| | |
|-----------------|---------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Predicted Height Standard Deviation Score (SDS) at Year 3 ^[13] |
|-----------------|---------------------------------------------------------------------------------------------------|

End point description:

Predicted height was calculated according to Greulich and Pyle using Bayley Pinneau method. Predicted height SDS was obtained by calculating the predicted height, subtracting chronological age- and gender-appropriate mean predicted height and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Year 3

Notes:

[13] - 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: Only descriptive data was planned to be reported for this endpoint.

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------|------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 ^[14] | 4 ^[15] | | |
| Units: SDS | | | | |
| median (full range (min-max)) | | | | |
| Baseline | -2.43 (-2.6 to -1.6) | -0.76 (-1.8 to 0.7) | | |
| Change at Year 3 | 1.63 (0.1 to 2.3) | 0.68 (-2.6 to 2) | | |

Notes:

[14] - Subjects who were evaluable for this measure.

[15] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Predicted Height Standard Deviation Score (SDS) at Final Height

| | |
|-----------------|---------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Predicted Height Standard Deviation Score (SDS) at Final Height ^[16] |
|-----------------|---------------------------------------------------------------------------------------------------------|

End point description:

Predicted height was calculated according to Greulich and Pyle using Bayley Pinneau method. Predicted height SDS was obtained by calculating the predicted height, subtracting chronological age- and gender-appropriate mean predicted height and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, final height (assessed up to Year 9.5)

Notes:

[16] - 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: Only descriptive data was planned to be reported for this endpoint.

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 ^[17] | 2 ^[18] | | |
| Units: SDS | | | | |
| median (full range (min-max)) | | | | |
| Baseline | -1.74 (-2.4 to -1.1) | -0.84 (-1.8 to 0.1) | | |
| Change at Final Height | 0.71 (0.1 to 1.3) | -0.67 (-2.4 to 1) | | |

Notes:

[17] - Subjects who were evaluable for this measure.

[18] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Insulin-like Growth Factor-1 (IGF-1) Concentration at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Insulin-like Growth Factor-1 (IGF-1) Concentration at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9 |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. Here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. Here "99999" in the median and full range values signifies not estimable (NA), since none of the subjects were available in the group "Somatropin (With Previous Somatropin Exposure)" at given time point.

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

End point timeframe:

Baseline, Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|----------------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: milligram per deciliter (mg/dL) | | | | |
| median (full range (min-max)) | | | | |
| Baseline (n = 10, 11) | 0.0165 (0.0075 to 0.0517) | 0.0361 (0.0181 to 0.0868) | | |
| Change at Year 0.5 (n = 10, 9) | 0.0255 (- 0.0145 to 0.039) | 0.0017 (- 0.0256 to 0.0681) | | |
| Change at Year 1 (n = 10, 11) | 0.0329 (- 0.0061 to 0.0531) | 0.0093 (- 0.0358 to 0.0488) | | |
| Change at Year 1.5 (n = 9, 11) | 0.0406 (- 0.0035 to 0.0754) | 0.0066 (- 0.0194 to 0.0599) | | |
| Change at Year 2 (n = 9, 10) | 0.0223 (0.0055 to 0.0673) | 0.0221 (- 0.0292 to 0.0534) | | |
| Change at Year 2.5 (n = 8, 8) | 0.0366 (- 0.0109 to 0.0558) | 0.0201 (- 0.0237 to 0.047) | | |
| Change at Year 3 (n = 9, 7) | 0.0445 (-0.006 to 0.0557) | 0.013 (-0.0049 to 0.0648) | | |
| Change at Year 3.5 (n = 7, 7) | 0.0396 (0.0014 to 0.0707) | 0.01 (-0.0022 to 0.0436) | | |
| Change at Year 4 (n = 7, 6) | 0.0453 (0.0175 to 0.0646) | 0.0212 (- 0.0014 to 0.0485) | | |
| Change at Year 4.5 (n = 6, 5) | 0.0431 (0.008 to 0.1233) | 0.0142 (0.0042 to 0.0303) | | |
| Change at Year 5 (n = 7, 5) | 0.0369 (0.0258 to 0.0902) | 0.0236 (0.0164 to 0.053) | | |
| Change at Year 5.5 (n = 5, 4) | 0.0448 (0.0258 to 0.0965) | 0.0186 (0.0119 to 0.0356) | | |
| Change at Year 6 (n = 5, 4) | 0.0454 (0.0155 to 0.0718) | 0.0256 (0 to 0.0434) | | |
| Change at Year 6.5 (n = 5, 2) | 0.0593 (0.0512 to 0.0766) | 0.0195 (0.0125 to 0.0264) | | |
| Change at Year 7 (n = 5, 1) | 0.0424 (0.0393 to 0.0766) | 0.0254 (0.0254 to 0.0254) | | |
| Change at Year 7.5 (n = 3, 0) | 0.0529 (0.0527 to 0.0599) | 99999 (99999 to 99999) | | |
| Change at Year 8 (n = 2, 0) | 0.0576 (0.0468 to 0.0683) | 99999 (99999 to 99999) | | |
| Change at Year 8.5 (n = 1, 0) | 0.028 (0.028 to 0.028) | 99999 (99999 to 99999) | | |
| Change at Year 9 (n = 1, 2) | 0.0403 (0.0403 to 0.0403) | 0.0363 (0.0159 to 0.0567) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Insulin-like Growth Factor Binding Protein 3 (IGFBP3) Concentration at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

| | |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Insulin-like Growth Factor Binding Protein 3 (IGFBP3) Concentration at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Baseline, Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[19] | 0 ^[20] | | |
| Units: mg/dL | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[19] - Data was not statistically summarized due to early termination of the study.

[20] - Data was not statistically summarized due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Lean Mass and Fat Mass at Year 1, 2, 3, 4, 5, 6, 7, 8 and 9

| | |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Lean Mass and Fat Mass at Year 1, 2, 3, 4, 5, 6, 7, 8 and 9 |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

Lean mass and fat mass: measurements of body composition assessed using Dual Energy X-ray Absorptiometry (DEXA) scan.

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

End point timeframe:

Baseline, Year 1, 2, 3, 4, 5, 6, 7, 8, 9

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[21] | 0 ^[22] | | |
| Units: kg | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[21] - Data was not statistically summarized due to early termination of the study.

[22] - Data was not statistically summarized due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone Mineralization at Year 1, 2, 3, 4, 5, 6, 7, 8 and 9

| | |
|-----------------|----------------------------------------------------------------------------------|
| End point title | Change from Baseline in Bone Mineralization at Year 1, 2, 3, 4, 5, 6, 7, 8 and 9 |
|-----------------|----------------------------------------------------------------------------------|

End point description:

Bone mineralization, an estimate of the amount of mineral (such as calcium) in the bone, was assessed using DEXA scan. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. Here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. Here "99999" in the median and full range values signifies not estimable (NA), since none of the subjects were available in the group "Somatropin (With Previous Somatropin Exposure)" at given time point.

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

End point timeframe:

Baseline, Year 1, 2, 3, 4, 5, 6, 7, 8, 9

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: grams | | | | |
| median (full range (min-max)) | | | | |
| Baseline (n = 10, 11) | 565.4 (136 to 1305) | 643 (454 to 998) | | |
| Change at Year 1 (n = 10, 11) | 104.67 (9 to 340) | 118.4 (-792.7 to 459.6) | | |
| Change at Year 2 (n = 9, 10) | 272.7 (63 to 590) | 231.3 (-47.5 to 774.4) | | |
| Change at Year 3 (n = 8, 7) | 375.27 (106 to 1084.9) | 403.8 (25 to 862.5) | | |
| Change at Year 4 (n = 3, 4) | 518.7 (450.8 to 1047.9) | 903.2 (277.1 to 1448.1) | | |

| | | | | |
|-----------------------------|---------------------------|---------------------------|--|--|
| Change at Year 5 (n = 7, 4) | 829 (421.7 to 1245.8) | 938.3 (591.8 to 1787.6) | | |
| Change at Year 6 (n = 5, 4) | 818.4 (112.5 to 1105.5) | 998.05 (371.4 to 1984.2) | | |
| Change at Year 7 (n = 5, 1) | 1206.1 (739.6 to 1437.3) | 1408.5 (1408.5 to 1408.5) | | |
| Change at Year 8 (n = 2, 0) | 1376 (1351.7 to 1400.4) | 99999 (99999 to 99999) | | |
| Change at Year 9 (n = 1, 2) | 1376.3 (1376.3 to 1376.3) | 1210.15 (898.6 to 1521.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Weight Standard Deviation Score (SDS) at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

| | |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Weight Standard Deviation Score (SDS) at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Body weight was measured using a balance scale. Weight SDS was obtained by measuring the weight, subtracting age- and gender-appropriate mean weight and dividing the result by standard deviation of that mean (as obtained from age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. Here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. Here "99999" in the median and full range values signifies not estimable (NA), since none of the subjects were available in the group "Somatropin (With Previous Somatropin Exposure)" at given time point.

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

End point timeframe:

Baseline, Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|--------------------------------|---------------------------------------------------|------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: SDS | | | | |
| median (full range (min-max)) | | | | |
| Baseline (n = 10, 11) | -2.06 (-4 to 2.6) | 0.04 (-5.4 to 5) | | |
| Change at Year 0.5 (n = 10, 9) | 0.25 (-0.7 to 0.4) | 0.06 (-0.8 to 1.2) | | |
| Change at Year 1 (n = 10, 11) | 0.31 (-0.1 to 1.5) | 0.25 (-1.1 to 0.9) | | |
| Change at Year 1.5 (n = 9, 11) | 0.62 (-0.3 to 2.3) | 0.34 (-1.6 to 2.3) | | |

| | | | | |
|-------------------------------|--------------------|------------------------|--|--|
| Change at Year 2 (n = 9, 10) | 1.23 (-0.2 to 2.7) | 0.46 (-1.1 to 2.2) | | |
| Change at Year 2.5 (n = 8, 8) | 1.51 (-0.9 to 3.2) | 0.77 (-1.1 to 2.6) | | |
| Change at Year 3 (n = 9, 7) | 1.48 (-1.9 to 3.7) | 0.61 (-1.2 to 2.7) | | |
| Change at Year 3.5 (n = 7, 7) | 1.56 (-1.9 to 3.7) | 0.78 (-1.3 to 3) | | |
| Change at Year 4 (n = 7, 6) | 1.96 (-2.3 to 3.8) | 0.58 (-1 to 2.4) | | |
| Change at Year 4.5 (n = 6, 5) | 1.78 (-2.7 to 4.1) | 1.46 (-0.4 to 2.7) | | |
| Change at Year 5 (n = 7, 5) | 2.08 (-3 to 3.9) | 2.06 (0.1 to 2.8) | | |
| Change at Year 5.5 (n = 5, 3) | 3.25 (1 to 3.8) | 2.1 (1.7 to 2.6) | | |
| Change at Year 6 (n = 5, 3) | 2.95 (1.2 to 4.4) | 1.89 (1.8 to 2.2) | | |
| Change at Year 6.5 (n = 5, 2) | 3.3 (0.8 to 5) | 2.03 (1.9 to 2.2) | | |
| Change at Year 7 (n = 5, 1) | 2.91 (0.2 to 5.2) | 1.7 (1.7 to 1.7) | | |
| Change at Year 7.5 (n = 3, 0) | 1.49 (0.3 to 3.1) | 99999 (99999 to 99999) | | |
| Change at Year 8 (n = 2, 0) | 1.06 (0.5 to 1.6) | 99999 (99999 to 99999) | | |
| Change at Year 8.5 (n = 1, 0) | 0.7 (0.7 to 0.7) | 99999 (99999 to 99999) | | |
| Change at Year 9 (n = 1, 1) | 1.4 (1.4 to 1.4) | 2 (2 to 2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Corticosteroid Dose at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Corticosteroid Dose at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9 |
|-----------------|--------------------------------------------------------------------------------------------------------------------------|

End point description:

FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. Here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. Here "99999" in the median and full range values signifies not estimable (NA), since none of the subjects were available in the group "Somatropin (With Previous Somatropin Exposure)" at given time point.

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

End point timeframe:

Baseline, Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9

| End point values | Somatropin (Without Previous Somatropin Exposure) | Somatropin (With Previous Somatropin Exposure) | | |
|--------------------------------|---------------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: mg | | | | |
| median (full range (min-max)) | | | | |
| Baseline (n = 10, 11) | 4.75 (2 to 13.5) | 7.5 (1 to 40) | | |
| Change at Year 0.5 (n = 10, 9) | 0 (-2.5 to 4.8) | 0 (-11 to 0) | | |
| Change at Year 1 (n = 9, 11) | -0.67 (-8.5 to 36) | 0 (-15 to 20.3) | | |
| Change at Year 1.5 (n = 8, 11) | 0.5 (-5 to 8.8) | 0 (-17 to 7.5) | | |
| Change at Year 2 (n = 8, 10) | -0.5 (-6.3 to 11.9) | 0 (-19 to 10.6) | | |
| Change at Year 2.5 (n = 7, 8) | 1.83 (-7.8 to 11.9) | 0.04 (-28 to 7.5) | | |
| Change at Year 3 (n = 7, 7) | 1.75 (-9.5 to 19.4) | 0 (-34.2 to 1) | | |
| Change at Year 3.5 (n = 6, 7) | 1.83 (-10.3 to 12.5) | -0.75 (-36 to 2.9) | | |
| Change at Year 4 (n = 7, 6) | 0.25 (-10 to 9.7) | -1.88 (-4.5 to 0) | | |
| Change at Year 4.5 (n = 6, 5) | 0.23 (-9 to 215.4) | -3.4 (-10 to 0) | | |
| Change at Year 5 (n = 7, 5) | -2 (-9.5 to 15) | -3.5 (-10 to -0.6) | | |
| Change at Year 5.5 (n = 5, 4) | 0.25 (-9.5 to 18.3) | -1.83 (-4.5 to 486.5) | | |
| Change at Year 6 (n = 5, 4) | -1 (-11 to 10.6) | -1.83 (-5.5 to 9) | | |
| Change at Year 6.5 (n = 5, 2) | -1 (-11 to 3) | -2.46 (-3.7 to -1.3) | | |
| Change at Year 7 (n = 5, 1) | -1 (-11 to 2) | -2.5 (-2.5 to -2.5) | | |
| Change at Year 7.5 (n = 3, 0) | -7 (-12 to 0.5) | 99999 (99999 to 99999) | | |
| Change at Year 8 (n = 2, 0) | -3.25 (-7 to 5) | 99999 (99999 to 99999) | | |
| Change at Year 8.5 (n = 1, 0) | 0.5 (0.5 to 0.5) | 99999 (99999 to 99999) | | |
| Change at Year 9 (n = 1, 2) | -7 (-7 to -7) | -3 (-3.5 to -2.5) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 7 days after last dose of study drug

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 1 subject and as nonserious in another, or 1 subject may have experienced both serious, nonserious event during study. EU BR specific AE tables were generated separately as per EU format using latest coding.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

Reporting groups

| | |
|-----------------------|------------------------------------------------|
| Reporting group title | Somatropin (With Previous Somatropin Exposure) |
|-----------------------|------------------------------------------------|

Reporting group description:

Subjects who received low dose of somatropin (Genotonorm) for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, equivalent to 1.8 IU/kg/week, divided in 7 daily doses subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, equivalent to 1.4 IU/kg/week, divided in 7 daily doses subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, equivalent to 0.35 mg/kg/week or 1.05 IU/kg/week, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was \leq 1.5 cm per year during the preceding 12 months and bone age was \geq 17 years for boys and 15 years for girls.

| | |
|-----------------------|---------------------------------------------------|
| Reporting group title | Somatropin (Without Previous Somatropin Exposure) |
|-----------------------|---------------------------------------------------|

Reporting group description:

Subjects who received matching placebo for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, equivalent to 1.8 IU/kg/week, divided in 7 daily doses subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, equivalent to 1.4 IU/kg/week, divided in 7 daily doses subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, equivalent to 0.35 mg/kg/week or 1.05 IU/kg/week, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was \leq 1.5 cm per year during the preceding 12 months and bone age was \geq 17 years for boys and 15 years for girls.

| Serious adverse events | Somatropin (With Previous Somatropin Exposure) | Somatropin (Without Previous Somatropin Exposure) | |
|---------------------------------------------------------------------|------------------------------------------------|---------------------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 11 (54.55%) | 2 / 10 (20.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|------------------------------------------------------|-----------------|-----------------|--|
| Surgical and medical procedures | | | |
| Gastrostomy closure | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth extraction | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |

| | | | |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Developmental hip dysplasia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Histiocytosis haematophagic | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Lipoatrophy | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Glomerulonephritis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Juvenile idiopathic arthritis | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteochondritis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |

| | | | |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scoliosis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Leishmaniasis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Relapsing fever | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Somatropin (With Previous Somatropin Exposure) | Somatropin (Without Previous Somatropin Exposure) | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 11 / 11 (100.00%) | 9 / 10 (90.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Melanocytic naevus subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) Poor peripheral circulation subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 | |
| Surgical and medical procedures Knee operation subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Ill-defined disorder subjects affected / exposed occurrences (all) Inflammation subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Injection site haemorrhage subjects affected / exposed occurrences (all) Nodule | 0 / 11 (0.00%) 0 2 / 11 (18.18%) 2 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 | 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 | |

| | | | |
|---------------------------------------------------------------------------------------------------------------|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Oedema subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 10 (10.00%) 1 | |
| Social circumstances Walking disability subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Reproductive system and breast disorders Gynaecomastia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Lung disorder subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Productive cough subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |

| | | | |
|------------------------------------------------|-----------------|-----------------|--|
| Insomnia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nightmare | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 10 (20.00%) | |
| occurrences (all) | 1 | 2 | |
| Investigations | | | |
| Blood corticotrophin decreased | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 10 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood glucose decreased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Glucose tolerance test | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 10 (20.00%) | |
| occurrences (all) | 0 | 2 | |
| Insulin-like growth factor increased | | | |
| subjects affected / exposed | 8 / 11 (72.73%) | 6 / 10 (60.00%) | |
| occurrences (all) | 17 | 12 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint injury | | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Ligament sprain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 2 / 10 (20.00%) 2 | |
| Procedural vomiting subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Congenital, familial and genetic disorders Congenital scoliosis subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | 0 / 10 (0.00%) 0 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Hyporeflexia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Hypotonia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Loss of consciousness subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Visual field defect subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Blood disorder subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Iron deficiency anaemia | | | |

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|------------------------------------------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Lymphadenopathy subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | 1 / 10 (10.00%) 1 | |
| Eye disorders | | | |
| Cataract subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 0 / 10 (0.00%) 0 | |
| Visual acuity reduced subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Aphthous stomatitis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Colitis subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Functional gastrointestinal disorder subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Gastritis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 10 (20.00%) 2 | |
| Hepatobiliary disorders | | | |
| Hepatomegaly subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| Acanthosis nigricans | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 10 (10.00%) | |
| occurrences (all) | 1 | 1 | |
| Acne | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 10 (10.00%) | |
| occurrences (all) | 1 | 1 | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Lividity | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pruritus generalised | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin atrophy | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Enuresis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 10 (20.00%) | |
| occurrences (all) | 0 | 2 | |
| Hypercalciuria | | | |

| | | | |
|------------------------------------------------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Renal colic subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 3 | 0 / 10 (0.00%) 0 | |
| Endocrine disorders Hyperparathyroidism subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Amyotrophy subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 10 (10.00%) 1 | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 3 | 3 / 10 (30.00%) 5 | |
| Arthritis subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | 1 / 10 (10.00%) 1 | |
| Back pain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 10 (0.00%) 0 | |
| Joint effusion subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 1 / 10 (10.00%) 1 | |
| Joint range of motion decreased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Juvenile idiopathic arthritis subjects affected / exposed occurrences (all) | 4 / 11 (36.36%) 6 | 4 / 10 (40.00%) 5 | |
| Osteonecrosis | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 3 / 10 (30.00%) | |
| occurrences (all) | 2 | 3 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 10 (20.00%) | |
| occurrences (all) | 1 | 2 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 10 (10.00%) | |
| occurrences (all) | 2 | 2 | |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 10 (20.00%) | |
| occurrences (all) | 0 | 2 | |
| Infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|------------------------------------|-----------------|-----------------|--|
| Laryngitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 10 (10.00%) | |
| occurrences (all) | 1 | 1 | |
| Nail candida | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 10 (20.00%) | |
| occurrences (all) | 0 | 4 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 2 / 10 (20.00%) | |
| occurrences (all) | 2 | 2 | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Otitis media | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 10 (10.00%) | |
| occurrences (all) | 1 | 1 | |
| Varicella | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Viral infection | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 10 (10.00%) | |
| occurrences (all) | 2 | 1 | |
| Metabolism and nutrition disorders | | | |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | 0 / 10 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Hyperinsulinaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Insulin resistance | | | |
| subjects affected / exposed | 6 / 11 (54.55%) | 5 / 10 (50.00%) | |
| occurrences (all) | 7 | 7 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 30 September 2004 | <p>1- Visits at month 3, month 9, month 15, month 21, month 27 and month 33 were not applicable for children who were not receiving Genotonorm due to the discontinuation of corticosteroid therapy.</p> <p>2- If corticosteroid therapy was discontinued in children at the beginning or during the study for at least 6 months and the height was greater than ($>$) -2 Standard Deviation (SD) for chronological age, then Genotonorm treatment was stopped and could only be resumed if corticosteroid therapy was resumed for at least 3 months and the investigative doctor considered it beneficial for the child.</p> <p>3- If 2 consecutive measurements of the level of IGF-1 were above 2 SD, then the daily dosage of Genotonorm was decreased by 20 percent (%).</p> <p>4- If the measurement of glucose in the urine was found to be above 10 gram/24 hours on 3 occasions, then the dosage of the growth hormone was decreased by 20% and further metabolic monitoring (fasting blood glucose and glucose in the urine) was done in the month following the dose change.</p> |
| 04 February 2005 | <p>1- Every year, following examinations were required to be performed in addition to examinations performed during a six-month visit: Serum calcium; serum phosphorus; 25 hydroxy (OH) vitamin D3 and 1.25 dihydroxy (OH)₂ vitamin D3 and Parathyroid hormone (PTH) levels; Oral glucose tolerance test (OGTT); Collection of 24-hour urine for calcium and creatinine; Collection of 2 mL of serum (4 x 0.5 mL); Bone age: radiography of 2 wrists.</p> <p>2- The maximum dose administered was reduced to 0.46 mg 1.4 IU/kg/week from 0.6 mg 1.8 IU/kg/week.</p> <p>3- Genotonorm treatment was adapted according to IGF-1 rates which were maintained below or equal to +2.5 SD for chronological age and If IGF-1 rates were above +2.5 SD the dose of growth hormone was decreased by 20%.</p> <p>4- In the case of diabetes defined by blood glucose at time T120 mins of OGTT ≥ 11.1 millimole per liter (mmol/L) or fasting blood glucose ≥ 7.0 mmol/L, the Genotonorm dose was reduced by 40% and another OGTT check was done after 3 months of dose adjustment. That diabetes was reported as an adverse event and If It persisted, Genotonorm treatment was interrupted and the event was reported as a serious adverse event.</p> |
| 29 November 2007 | Genotonorm treatment was adapted according to IGF-1 levels which were maintained below or equal to +2 SD for chronological age and sex and If IGF-1 level was above +2 SD, then the growth hormone dose was decreased by 20%. |
| 16 February 2011 | The maximal dose of somatropin was limited up to 50 mcg/kg/day (0.35 mg [1.05 IU/kg/week]) in relation to the ongoing review of safety of somatropin- containing products. |

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.

Data for bone mineral density (BMD), bone mineral content (BMC) and IGFBP3 were not analyzed because of change in planned analysis after the study was prematurely terminated due to Good Clinical Practice (GCP) non-compliance issues.

Notes: