



## Clinical trial results:

### A Four-Year Open-Label Multi-Center Randomized Two-Arm Study Of Genotropin In Idiopathic Short Stature Patients: Comparing An Individualized, Target-Driven Treatment Regimen To Standard Dosing Of Genotropin

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-004172-32 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 30 August 2012 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 27 April 2016  |
| First version publication date | 01 August 2015 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A6281280 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00396097 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Pfizer   |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, 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:

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**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 08 February 2013 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 August 2012   |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

To demonstrate that an individualized, formula-based Genotropin regimen for children with Idiopathic Short Stature (ISS) will lead to a targeted height gain (to reach the target of 10th percentile (%), or - 1.3 Standard Deviation Score (SDS)) during 24 months of treatment.

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                          | 08 December 2006 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 316 |
| Worldwide total number of subjects   | 316                |
| EEA total number of subjects         | 0                  |

Notes:

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**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)                     | 292 |
| Adolescents (12-17 years)                 | 24  |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This was a 4-year, open-label, randomized study conducted at 40 centers across United States of America (USA). The first 2-years of the study constituted core phase and the last 2 years constituted the maintenance phase.

### Pre-assignment

Screening details:

The subjects were randomized in 2:1 manner to formula-based dosing arm and standard dosing arm for initial 2 years of treatment, following which the subjects in formula-based dosing arm were re-randomized in a 1:1 manner to one of two physiological doses, for next 2 years, to identify the minimum genotropin dosage to maintain the growth.

### Period 1

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

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | Standard Dose Arm |

Arm description:

The subjects received subcutaneous genotropin throughout the four years.

|  |  |
|--|--|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Genotropin   |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder and solvent for solution for injection in cartridge |
| Routes of administration               | Subcutaneous use   |

Dosage and administration details:

The subjects received subcutaneous genotropin daily, at maintained standard dose of 0.37 milligram per kilogram per week (mg/kg/week), throughout the four years.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Individualized Dose Arm |
|------------------|-------------------------|

Arm description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose for the initial 2 years and then lowered to physiological doses for the remaining 2 years.

|  |   |
|--|---|
| Arm type                               | Active comparator                             |
| Investigational medicinal product name | Genotropin                                    |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Subcutaneous use                              |

Dosage and administration details:

The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses (0.18 mg/kg/week or 0.24 mg/kg/week) for the remaining 2 years.

| <b>Number of subjects in period 1</b> | Standard Dose Arm | Individualized Dose Arm |
|---------------------------------------|-------------------|-------------------------|
| Started                               | 114               | 202                     |
| Completed                             | 88                | 156                     |
| Not completed                         | 26                | 46                      |
| Consent withdrawn by subject          | 17                | 17                      |
| Adverse event, non-fatal              | 1                 | 5                       |
| Not specified                         | 3                 | 5                       |
| Insufficient Clinical Response        | 1                 | 4                       |
| Lost to follow-up                     | 4                 | 9                       |
| Protocol deviation                    | -                 | 6                       |

## Baseline characteristics

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Standard Dose Arm |
|-----------------------|-------------------|

Reporting group description:

The subjects received subcutaneous genotropin throughout the four years.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Individualized Dose Arm |
|-----------------------|-------------------------|

Reporting group description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose for the initial 2 years and then lowered to physiological doses for the remaining 2 years.

| Reporting group values                     | Standard Dose Arm | Individualized Dose Arm | Total |
|--|-------------------|-------------------------|-------|
| Number of subjects                         | 114               | 202                     | 316   |
| Age, Customized<br>Units: Participants     |                   |                         |       |
| <= 7 years                                 | 37                | 70                      | 107   |
| >=7 years                                  | 77                | 132                     | 209   |
| Age Continuous<br>Units: years             |                   |                         |       |
| arithmetic mean                            | 8.3               | 8.4                     |       |
| standard deviation                         | ± 2.1             | ± 2.3                   | -     |
| Gender, Male/Female<br>Units: Participants |                   |                         |       |
| Female                                     | 31                | 58                      | 89    |
| Male                                       | 83                | 144                     | 227   |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Standard Dose Arm                       |
| Reporting group description:<br>The subjects received subcutaneous genotropin throughout the four years.   |   |
| Reporting group title  | Individualized Dose Arm                 |
| Reporting group description:<br>The subjects received subcutaneous genotropin daily, at formula-calculated dose for the initial 2 years and then lowered to physiological doses for the remaining 2 years.   |   |
| Subject analysis set title   | Individualized Dose Arm Overall         |
| Subject analysis set type  | Full analysis                           |
| Subject analysis set description:<br>The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses (0.18 mg/kg/week or 0.24 mg/kg/week) for the remaining 2 years. |   |
| Subject analysis set title   | Individualized Dose Arm 0.18 mg/kg/Week |
| Subject analysis set type  | Full analysis                           |
| Subject analysis set description:<br>The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses 0.18 mg/kg/week for the remaining 2 years.                      |   |
| Subject analysis set title   | Individualized Dose Arm 0.24 mg/kg/Week |
| Subject analysis set type  | Full analysis                           |
| Subject analysis set description:<br>The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses 0.24 mg/kg/week for the remaining 2 years.                      |   |

### Primary: Absolute on-target Difference (AOTD) at 24 Months

|  |   |
|--|---|
| End point title  | Absolute on-target Difference (AOTD) at 24 Months |
| End point description:<br>This was defined as an absolute difference between the 24-month height standard deviation score (SDS) and targeted 24-month height SDS (10th percentile (%), or -1.3 SDS). SDS indicates how similar the subjects was to the reference population. These were calculated using 2000 Center for the Disease Control (CDC) growth reference tables (by age and gender). The Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. Last observation carried forward (LOCF) rule was applied to impute Month 24 missing height SDS data. |   |
| End point type   | Primary   |
| End point timeframe:<br>2 years  |   |

| End point values                      | Standard Dose Arm     | Individualized Dose Arm |  |  |
|---------------------------------------|-----------------------|-------------------------|--|--|
| Subject group type                    | Reporting group       | Reporting group         |  |  |
| Number of subjects analysed           | 114                   | 202                     |  |  |
| Units: Standard Deviation Score (SDS) |                       |                         |  |  |
| arithmetic mean (standard deviation)  | 0.603 ( $\pm$ 0.2948) | 0.625 ( $\pm$ 0.3003)   |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Absolute On-target Difference (AOTD) at 24 Months |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm       |
| Number of subjects included in analysis | 316   |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | superiority                                       |
| P-value                                 | = 0.5762  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                    |
| Point estimate                          | -0.006  |
| Confidence interval                     |   |
| level                                   | Other: 97.5 %                                     |
| sides                                   | 1-sided   |
| lower limit                             | -0.071  |
| Variability estimate                    | Standard error of the mean                        |
| Dispersion value                        | 0.033   |

## Secondary: Variability of Height SDS at 24 Months

|   |  |
|---|--|
| End point title   | Variability of Height SDS at 24 Months |
| End point description:  |  |
| The continuous endpoint of variability of height SDS at 24 months was defined as the SD of the 24 month height SDS. FAS included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. LOCF rule was applied to impute Month 24 missing height SDS data. |  |
| End point type  | Secondary                              |
| End point timeframe:  |  |
| 2 years   |  |

| End point values                              | Standard Dose Arm   | Individualized Dose Arm |  |  |
|---|---------------------|-------------------------|--|--|
| Subject group type                            | Reporting group     | Reporting group         |  |  |
| Number of subjects analysed                   | 114                 | 202                     |  |  |
| Units: Standard Deviation Score (SDS)         |                     |                         |  |  |
| arithmetic mean (standard deviation)          |                     |                         |  |  |
| Change from baseline at 24 months (n=101,184) | 1.12 ( $\pm$ 0.408) | 1.11 ( $\pm$ 0.518)     |  |  |

|   |                     |                     |  |  |
|---|---------------------|---------------------|--|--|
| Change from baseline at 24 months<br>LOCF (n=114,202) | 1.03 ( $\pm$ 0.475) | 1.04 ( $\pm$ 0.544) |  |  |
|---|---------------------|---------------------|--|--|

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Variability of Height SDS at 24 Months      |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm |
| Number of subjects included in analysis | 316   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | superiority                                 |
| P-value                                 | = 0.627                                     |
| Method                                  | ANOVA (Levene's Test)                       |

### Secondary: Time Cost (Months Until greater than or equal to ( $\geq$ ) -2 SDS)

|   |   |
|---|---|
| End point title   | Time Cost (Months Until greater than or equal to ( $\geq$ ) -2 SDS) |
| End point description:<br>Time cost was defined as the number of months needed until height SDS was within the normal limit (ie, greater than or equal to ( $\geq$ ) -2 SDS). FAS included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. |   |
| End point type  | Secondary   |
| End point timeframe:<br>2 years   |   |

|                                  |                   |                         |  |  |
|----------------------------------|-------------------|-------------------------|--|--|
| <b>End point values</b>          | Standard Dose Arm | Individualized Dose Arm |  |  |
| Subject group type               | Reporting group   | Reporting group         |  |  |
| Number of subjects analysed      | 114               | 202                     |  |  |
| Units: Months                    |                   |                         |  |  |
| median (confidence interval 95%) | 12 (8 to 12)      | 12 (8 to 12)            |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Time Cost (Months Until $\geq$ -2 SDS)      |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm |
| Number of subjects included in analysis | 316   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | superiority                                 |
| P-value                                 | = 0.8016                                    |
| Method                                  | Regression, Cox                             |
| Parameter estimate                      | Hazard ratio (HR)                           |
| Point estimate                          | 1.033                                       |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.802   |
| upper limit         | 1.33    |

## Secondary: Computed Cost of Height Gain at 48 Months

|   |  |
|---|--|
| End point title   | Computed Cost of Height Gain at 48 Months <sup>[1]</sup> |
| End point description:  |  |
| The computed cost of height gain was defined as the amount of drug used relative to the observed height-gain, in terms of milligram per centimeter (mg/cm) , this was calculated at Month 48. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| 4 years   |  |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Data was not collected at the end of study visit for Individual Dose Arm as comparison between the groups was not planned.

| End point values                     | Standard Dose Arm | Individualized Dose Arm Overall | Individualized Dose Arm 0.18 mg/kg/Week | Individualized Dose Arm 0.24 mg/kg/Week |
|--------------------------------------|-------------------|---------------------------------|---|---|
| Subject group type                   | Reporting group   | Subject analysis set            | Subject analysis set                    | Subject analysis set                    |
| Number of subjects analysed          | 114               | 202                             | 91                                      | 88                                      |
| Units: mg/cm                         |                   |                                 |   |   |
| arithmetic mean (standard deviation) | 72.77 (± 17.914)  | 67.3 (± 24.382)                 | 63.07 (± 21.656)                        | 69.62 (± 21.903)                        |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Height Gain at 48 Months                            |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm Overall |
| Number of subjects included in analysis | 316   |
| Analysis specification                  | Pre-specified                                       |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0101  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                      |
| Point estimate                          | 5.822   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.395   |
| upper limit                             | 10.249  |
| Variability estimate                    | Standard error of the mean                          |
| Dispersion value                        | 2.25  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Height Gain at 48 Months: 0.18 mg/kg/week                   |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm 0.18 mg/kg/Week |
| Number of subjects included in analysis | 205   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0002  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                              |
| Point estimate                          | 9.281   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 4.417   |
| upper limit                             | 14.145  |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 2.471   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Height Gain at 48 Months: 0.24 mg/kg/week                   |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm 0.24 mg/kg/Week |
| Number of subjects included in analysis | 202   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.2001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                              |
| Point estimate                          | 3.204   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -1.707  |
| upper limit                             | 8.114   |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 2.495   |

## Secondary: Estimated Cost of Height Gain Estimated Until Full Adult Height (FAH) at 48 Months

|                 |   |
|-----------------|---|
| End point title | Estimated Cost of Height Gain Estimated Until Full Adult Height (FAH) at 48 Months <sup>[2]</sup> |
|-----------------|---|

### End point description:

The estimated cost of long-term height gain until FAH was calculated. FAS included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. LOCF rule was applied to impute Month 24 missing height SDS data.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| 4 years  |           |
| Notes:   |           |
| [2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: Data was not collected at the end of study visit for Individual Dose Arm as comparison between the groups was not planned. |           |

| End point values                     | Standard Dose Arm      | Individualized Dose Arm Overall | Individualized Dose Arm 0.18 mg/kg/Week | Individualized Dose Arm 0.24 mg/kg/Week |
|--------------------------------------|------------------------|---------------------------------|---|---|
| Subject group type                   | Reporting group        | Subject analysis set            | Subject analysis set                    | Subject analysis set                    |
| Number of subjects analysed          | 112                    | 192                             | 90                                      | 88                                      |
| Units: mg/cm                         |                        |                                 |   |   |
| arithmetic mean (standard deviation) | 127.99 ( $\pm$ 29.708) | 91.34 ( $\pm$ 31.854)           | 80.06 ( $\pm$ 21)                       | 92.24 ( $\pm$ 25.213)                   |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Full Adult Height                                   |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm Overall |
| Number of subjects included in analysis | 304   |
| Analysis specification                  | Pre-specified                                       |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                      |
| Point estimate                          | 36.899  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 30.181  |
| upper limit                             | 43.618  |
| Variability estimate                    | Standard error of the mean                          |
| Dispersion value                        | 3.414   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Full Adult Height: 0.18mg/kg/Week                           |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm 0.18 mg/kg/Week |
| Number of subjects included in analysis | 202   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                              |
| Point estimate                          | 48.517  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | 42.054                     |
| upper limit          | 54.98                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 3.284                      |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Full Adult Height: 0.24 mg/kg/Week                          |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm 0.24 mg/kg/Week |
| Number of subjects included in analysis | 200   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                              |
| Point estimate                          | 34.443  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 27.936  |
| upper limit                             | 40.951  |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 3.306   |

### Secondary: Change From Baseline in Height SDS at 48 Months.

|   |   |
|---|---|
| End point title   | Change From Baseline in Height SDS at 48 Months. <sup>[3]</sup> |
| End point description:  |   |
| Change in height SDS was measured at 48 months. FAS included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. LOCF rule was applied to impute Month 24 missing height SDS data.   |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| 4 years   |   |
| Notes:  |   |
| [3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data was not collected at the end of study visit for Individual Dose Arm as comparison between the groups was not planned. |   |

| End point values                      | Standard Dose Arm | Individualized Dose Arm Overall | Individualized Dose Arm 0.18 mg/kg/Week | Individualized Dose Arm 0.24 mg/kg/Week |
|---------------------------------------|-------------------|---------------------------------|---|---|
| Subject group type                    | Reporting group   | Subject analysis set            | Subject analysis set                    | Subject analysis set                    |
| Number of subjects analysed           | 114               | 202                             | 91                                      | 88                                      |
| Units: Standard Deviation Score (SDS) |                   |                                 |   |   |
| arithmetic mean (standard deviation)  | 1.33 (± 0.717)    | 1.24 (± 0.668)                  | 1.33 (± 0.637)                          | 1.34 (± 0.633)                          |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change From Baseline in Height SDS                  |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm Overall |
| Number of subjects included in analysis | 316   |
| Analysis specification                  | Pre-specified                                       |
| Analysis type                           | superiority   |
| P-value                                 | = 0.2618  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                      |
| Point estimate                          | 0.091   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.068  |
| upper limit                             | 0.249   |
| Variability estimate                    | Standard error of the mean                          |
| Dispersion value                        | 0.081   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change From Baseline in Height SDS: 0.18mg/kg/Week          |
| Comparison groups                       | Standard Dose Arm v Individualized Dose Arm 0.18 mg/kg/Week |
| Number of subjects included in analysis | 205   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.8926  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)                              |
| Point estimate                          | 0.013   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.172  |
| upper limit                             | 0.198   |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 0.094   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Change From Baseline in Height SDS: 0.24mg/kg/Week          |
| Comparison groups                 | Standard Dose Arm v Individualized Dose Arm 0.24 mg/kg/Week |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 202                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.9566                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.005                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.192                         |
| upper limit                             | 0.181                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.095                          |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

4 years

Adverse event reporting additional description:

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

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Standard Dose Arm |
|-----------------------|-------------------|

Reporting group description:

The subjects received subcutaneous genotropin daily, at a maintained standard dose of 0.37 mg/kg/week, throughout the four years.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Individualized Dose Arm |
|-----------------------|-------------------------|

Reporting group description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses (0.18 mg/kg/week or 0.24 mg/kg/week) for the remaining 2 years.

| Serious adverse events                            | Standard Dose Arm | Individualized Dose Arm |  |
|---|-------------------|-------------------------|--|
| Total subjects affected by serious adverse events |                   |                         |  |
| subjects affected / exposed                       | 13 / 118 (11.02%) | 7 / 198 (3.54%)         |  |
| number of deaths (all causes)                     | 0                 | 0                       |  |
| number of deaths resulting from adverse events    |                   |                         |  |
| Injury, poisoning and procedural complications    |                   |                         |  |
| Accident  |                   |                         |  |
| subjects affected / exposed                       | 1 / 118 (0.85%)   | 0 / 198 (0.00%)         |  |
| occurrences causally related to treatment / all   | 0 / 1             | 0 / 0                   |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0                   |  |
| Craniocerebral injury                             |                   |                         |  |
| subjects affected / exposed                       | 1 / 118 (0.85%)   | 0 / 198 (0.00%)         |  |
| occurrences causally related to treatment / all   | 0 / 1             | 0 / 0                   |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0                   |  |
| Facial bones fracture                             |                   |                         |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 198 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foreign Body                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 198 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fracture  |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 198 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 198 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Arnold-chiari malformation                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 198 (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                        |                 |                 |  |
| Convulsion                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 1 / 198 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracranial pressure increased                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 198 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumocephalus                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 198 (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 |                 |                 |  |
| Device breakage                                      |                 |                 |  |
| subjects affected / exposed                          | 0 / 118 (0.00%) | 1 / 198 (0.51%) |  |
| 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 / 118 (0.85%) | 0 / 198 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 118 (0.85%) | 0 / 198 (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      |                 |                 |  |
| Asthma   |                 |                 |  |
| subjects affected / exposed                          | 2 / 118 (1.69%) | 0 / 198 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                                |                 |                 |  |
| Abnormal behaviour                                   |                 |                 |  |
| subjects affected / exposed                          | 0 / 118 (0.00%) | 1 / 198 (0.51%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Affective disorder                                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 118 (0.85%) | 0 / 198 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders      |                 |                 |  |
| Scoliosis  |                 |                 |  |
| subjects affected / exposed                          | 1 / 118 (0.85%) | 0 / 198 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Infections and infestations                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 1 / 198 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 118 (1.69%) | 0 / 198 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 198 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Standard Dose Arm  | Individualized Dose Arm |  |
|---|--------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events |                    |                         |  |
| subjects affected / exposed                           | 103 / 118 (87.29%) | 165 / 198 (83.33%)      |  |
| Nervous system disorders                              |                    |                         |  |
| Headache  |                    |                         |  |
| subjects affected / exposed                           | 33 / 118 (27.97%)  | 59 / 198 (29.80%)       |  |
| occurrences (all)                                     | 71                 | 147                     |  |
| Blood and lymphatic system disorders                  |                    |                         |  |
| Lymphadenopathy                                       |                    |                         |  |
| subjects affected / exposed                           | 5 / 118 (4.24%)    | 13 / 198 (6.57%)        |  |
| occurrences (all)                                     | 8                  | 19                      |  |
| General disorders and administration site conditions  |                    |                         |  |
| Pyrexia   |                    |                         |  |
| subjects affected / exposed                           | 13 / 118 (11.02%)  | 22 / 198 (11.11%)       |  |
| occurrences (all)                                     | 14                 | 35                      |  |
| Immune system disorders                               |                    |                         |  |
| Hypersensitivity                                      |                    |                         |  |
| subjects affected / exposed                           | 6 / 118 (5.08%)    | 6 / 198 (3.03%)         |  |
| occurrences (all)                                     | 12                 | 9                       |  |
| Gastrointestinal disorders                            |                    |                         |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 2 / 118 (1.69%)<br>2    | 10 / 198 (5.05%)<br>15  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 6 / 118 (5.08%)<br>7    | 6 / 198 (3.03%)<br>9    |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 9 / 118 (7.63%)<br>11   | 17 / 198 (8.59%)<br>19  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 7 / 118 (5.93%)<br>7    | 12 / 198 (6.06%)<br>12  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 5 / 118 (4.24%)<br>5    | 11 / 198 (5.56%)<br>13  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 15 / 118 (12.71%)<br>20 | 21 / 198 (10.61%)<br>30 |  |
| Respiratory, thoracic and mediastinal disorders                          |                         |                         |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                | 8 / 118 (6.78%)<br>10   | 26 / 198 (13.13%)<br>36 |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)     | 10 / 118 (8.47%)<br>14  | 17 / 198 (8.59%)<br>26  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)   | 6 / 118 (5.08%)<br>11   | 19 / 198 (9.60%)<br>26  |  |
| Musculoskeletal and connective tissue disorders                          |                         |                         |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 15 / 118 (12.71%)<br>24 | 24 / 198 (12.12%)<br>33 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)    | 14 / 118 (11.86%)<br>19 | 17 / 198 (8.59%)<br>42  |  |
| Scoliosis  |                         |                         |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 11 / 118 (9.32%)<br>11 | 19 / 198 (9.60%)<br>20 |  |
| Infections and infestations                      |                        |                        |  |
| Ear infection                                    |                        |                        |  |
| subjects affected / exposed                      | 1 / 118 (0.85%)        | 11 / 198 (5.56%)       |  |
| occurrences (all)                                | 1                      | 17                     |  |
| Gastroenteritis                                  |                        |                        |  |
| subjects affected / exposed                      | 10 / 118 (8.47%)       | 11 / 198 (5.56%)       |  |
| occurrences (all)                                | 13                     | 18                     |  |
| Gastroenteritis viral                            |                        |                        |  |
| subjects affected / exposed                      | 7 / 118 (5.93%)        | 15 / 198 (7.58%)       |  |
| occurrences (all)                                | 7                      | 17                     |  |
| Influenza  |                        |                        |  |
| subjects affected / exposed                      | 16 / 118 (13.56%)      | 22 / 198 (11.11%)      |  |
| occurrences (all)                                | 18                     | 30                     |  |
| Nasopharyngitis                                  |                        |                        |  |
| subjects affected / exposed                      | 8 / 118 (6.78%)        | 25 / 198 (12.63%)      |  |
| occurrences (all)                                | 25                     | 54                     |  |
| Otitis externa                                   |                        |                        |  |
| subjects affected / exposed                      | 2 / 118 (1.69%)        | 10 / 198 (5.05%)       |  |
| occurrences (all)                                | 2                      | 13                     |  |
| Otitis media                                     |                        |                        |  |
| subjects affected / exposed                      | 11 / 118 (9.32%)       | 23 / 198 (11.62%)      |  |
| occurrences (all)                                | 12                     | 29                     |  |
| Pharyngitis streptococcal                        |                        |                        |  |
| subjects affected / exposed                      | 15 / 118 (12.71%)      | 30 / 198 (15.15%)      |  |
| occurrences (all)                                | 23                     | 47                     |  |
| Sinusitis  |                        |                        |  |
| subjects affected / exposed                      | 9 / 118 (7.63%)        | 23 / 198 (11.62%)      |  |
| occurrences (all)                                | 20                     | 47                     |  |
| Upper respiratory tract infection                |                        |                        |  |
| subjects affected / exposed                      | 28 / 118 (23.73%)      | 45 / 198 (22.73%)      |  |
| occurrences (all)                                | 52                     | 73                     |  |
| Viral infection                                  |                        |                        |  |
| subjects affected / exposed                      | 9 / 118 (7.63%)        | 11 / 198 (5.56%)       |  |
| occurrences (all)                                | 11                     | 13                     |  |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported