



## Clinical trial results:

### **RECOMBINANT HUMAN GROWTH HORMONE (RHGH) AND RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR-1 (RHIGF-1) COMBINATION THERAPY IN CHILDREN WITH SHORT STATURE ASSOCIATED WITH IGF-1 DEFICIENCY: A SIX-YEAR, RANDOMIZED, MULTI-CENTER, OPEN LABEL, PARALLEL-GROUP, ACTIVE TREATMENT CONTROLLED, DOSE SELECTION TRIAL.**

#### **Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-000843-29 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 01 March 2012  |

#### **Results information**

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 22 September 2019 |
| First version publication date | 22 September 2019 |

#### **Trial information**

##### **Trial identification**

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | MS316 |
|-----------------------|-------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00572156 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### **Sponsors**

|                              |                                                            |
|------------------------------|------------------------------------------------------------|
| Sponsor organisation name    | Ipsen Pharma                                               |
| Sponsor organisation address | 65 Quai Georges Gorse, Boulogne Billancourt, France, 92100 |
| Public contact               | Medical Director, Ipsen Pharma, clinical.trials@ipsen.com  |
| Scientific contact           | Medical Director, Ipsen Pharma, clinical.trials@ipsen.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                       | 01 March 2012 |
| Is this the analysis of the primary completion data? | No            |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 01 March 2012 |
| Was the trial ended prematurely? | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy and safety of three combinations of recombinant human growth hormone (rhGH) and recombinant human insulin-like growth factor-1 (rhIGF-1) compared to that of rhGH alone in the treatment of short stature associated with IGF-1 deficiency.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice, the ethical principles that have their origins in the Declaration of Helsinki, and applicable national and local regulatory requirements.

Background therapy: -

Evidence for comparator:

Under standard United States (US) clinical practice, children in this study could expect to be prescribed long-term rhGH treatment following a diagnosis of idiopathic short stature. The use of a placebo group would be unethical where a viable treatment option exists; hence rhGH monotherapy (45 micrograms per kilogram [ $\mu\text{g/kg}$ ] per day) was included as a comparator in this study.

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 01 January 2008 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 106 |
| Worldwide total number of subjects   | 106                |
| EEA total number of subjects         | 0                  |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 95 |
| Adolescents (12-17 years)                 | 11 |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

#### Recruitment details:

This was a Phase II, multicenter, randomized, open-label, parallel-group, active treatment controlled, dose selection study in prepubertal children, aged  $\geq 5$  years, with short stature associated with low IGF-1 and normal stimulated GH response. The study was conducted at 27 centers in the US from January 2008 to March 2012.

### Pre-assignment

#### Screening details:

Eligible subjects were randomized to one of four treatment groups, stratified by age  $\leq 9$  years and IGF-1 standard deviation score (SDS)  $\leq -2$ , in a 1:1:1:1 ratio. The planned treatment duration for each subject was six years, however, the study was prematurely terminated by the Sponsor after the last subject completed Year 3.

### 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>             | 45 µg/kg rhGH Alone |

#### Arm description:

Subjects received 45 µg/kg rhGH alone, administered once daily by injection. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Active comparator        |
| Investigational medicinal product name | rhGH                     |
| Investigational medicinal product code |                          |
| Other name                             | Somatropin, Nutropin AQ® |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |

#### Dosage and administration details:

Subjects received subcutaneous injections of rhGH once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to rotate the injection sites daily to minimize the potential for injection site reactions.

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 |
|------------------|----------------------------------|

#### Arm description:

Subjects received 45 µg/kg rhGH and 50 µg/kg rhIGF-1, administered once daily as separate injections. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | rhGH                     |
| Investigational medicinal product code |                          |
| Other name                             | Somatropin, Nutropin AQ® |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |

#### Dosage and administration details:

Subjects received subcutaneous injections of rhGH once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | rhIGF-1                |
| Investigational medicinal product code |                        |
| Other name                             | Mecasermin, Increlex®  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

Subjects received subcutaneous injections of rhIGF-1 once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 |
|------------------|-----------------------------------|

**Arm description:**

Subjects received 45 µg/kg rhGH and 100 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | rhGH                     |
| Investigational medicinal product code |                          |
| Other name                             | Somatropin, Nutropin AQ® |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |

**Dosage and administration details:**

Subjects received subcutaneous injections of rhGH once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | rhIGF-1                |
| Investigational medicinal product code |                        |
| Other name                             | Mecasermin, Increlex®  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

Subjects received subcutaneous injections of rhIGF-1 once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
|------------------|-----------------------------------|

**Arm description:**

Subjects received 45 µg/kg rhGH and 150 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned doses. Full doses commenced on the day immediately following Day 15 (Visit 3).

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | rhGH                     |
| Investigational medicinal product code |                          |
| Other name                             | Somatropin, Nutropin AQ® |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |

**Dosage and administration details:**

Subjects received subcutaneous injections of rhGH once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | rhIGF-1                |
| Investigational medicinal product code |                        |
| Other name                             | Mecasermin, Increlex®  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Subjects received subcutaneous injections of rhIGF-1 once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

| <b>Number of subjects in period 1</b> | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH + 50<br>µg/kg rhIGF-1 | 45 µg/kg rhGH +<br>100 µg/kg rhIGF-1 |
|---------------------------------------|------------------------|-------------------------------------|--------------------------------------|
| Started                               | 26                     | 27                                  | 27                                   |
| Completed                             | 0                      | 1                                   | 0                                    |
| Not completed                         | 26                     | 26                                  | 27                                   |
| Adverse event, non-fatal              | 3                      | 1                                   | 5                                    |
| Subject/Parent Decision               | 1                      | 6                                   | 4                                    |
| Sponsor Decision                      | 20                     | 16                                  | 17                                   |
| Lost to follow-up                     | 1                      | 1                                   | 1                                    |
| Protocol deviation                    | 1                      | 2                                   | -                                    |

| <b>Number of subjects in period 1</b> | 45 µg/kg rhGH +<br>150 µg/kg rhIGF-1 |
|---------------------------------------|--------------------------------------|
| Started                               | 26                                   |
| Completed                             | 1                                    |
| Not completed                         | 25                                   |
| Adverse event, non-fatal              | 1                                    |
| Subject/Parent Decision               | 3                                    |
| Sponsor Decision                      | 19                                   |
| Lost to follow-up                     | -                                    |
| Protocol deviation                    | 2                                    |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                        |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                  | 45 µg/kg rhGH Alone               |
| Reporting group description:<br>Subjects received 45 µg/kg rhGH alone, administered once daily by injection.<br>Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).                            |                                   |
| Reporting group title                                                                                                                                                                                                                                                                  | 45 µg/kg rhGH + 50 µg/kg rhIGF-1  |
| Reporting group description:<br>Subjects received 45 µg/kg rhGH and 50 µg/kg rhIGF-1, administered once daily as separate injections.<br>Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).   |                                   |
| Reporting group title                                                                                                                                                                                                                                                                  | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 |
| Reporting group description:<br>Subjects received 45 µg/kg rhGH and 100 µg/kg rhIGF-1, administered once daily as separate injections.<br>Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).  |                                   |
| Reporting group title                                                                                                                                                                                                                                                                  | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
| Reporting group description:<br>Subjects received 45 µg/kg rhGH and 150 µg/kg rhIGF-1, administered once daily as separate injections.<br>Treatment commenced on Day 1 (Visit 2) at 50% of the assigned doses. Full doses commenced on the day immediately following Day 15 (Visit 3). |                                   |

| Reporting group values | 45 µg/kg rhGH Alone | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 |
|------------------------|---------------------|----------------------------------|-----------------------------------|
| Number of subjects     | 26                  | 27                               | 27                                |
| Age categorical        |                     |                                  |                                   |
| Units: Subjects        |                     |                                  |                                   |

|                                     |       |       |       |
|-------------------------------------|-------|-------|-------|
| Age continuous                      |       |       |       |
| Units: years                        |       |       |       |
| arithmetic mean                     | 9.2   | 8.4   | 9.0   |
| standard deviation                  | ± 2.0 | ± 2.0 | ± 2.2 |
| Gender categorical                  |       |       |       |
| Units: Subjects                     |       |       |       |
| Female                              | 5     | 5     | 7     |
| Male                                | 21    | 22    | 20    |
| Race                                |       |       |       |
| Units: Subjects                     |       |       |       |
| Asian                               | 2     | 4     | 1     |
| Black                               | 1     | 1     | 1     |
| Hispanic                            | 4     | 1     | 3     |
| White                               | 17    | 20    | 19    |
| Hispanic/White                      | 1     | 1     | 3     |
| Hawaiian or Pacific Islander/ White | 1     | 0     | 0     |

| Reporting group values | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 | Total |  |
|------------------------|-----------------------------------|-------|--|
| Number of subjects     | 26                                | 106   |  |

|                                     |       |    |  |
|-------------------------------------|-------|----|--|
| Age categorical                     |       |    |  |
| Units: Subjects                     |       |    |  |
| Age continuous                      |       |    |  |
| Units: years                        |       |    |  |
| arithmetic mean                     | 8.8   |    |  |
| standard deviation                  | ± 2.3 | -  |  |
| Gender categorical                  |       |    |  |
| Units: Subjects                     |       |    |  |
| Female                              | 4     | 21 |  |
| Male                                | 22    | 85 |  |
| Race                                |       |    |  |
| Units: Subjects                     |       |    |  |
| Asian                               | 1     | 8  |  |
| Black                               | 0     | 3  |  |
| Hispanic                            | 2     | 10 |  |
| White                               | 23    | 79 |  |
| Hispanic/White                      | 0     | 5  |  |
| Hawaiian or Pacific Islander/ White | 0     | 1  |  |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                        |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                  | 45 µg/kg rhGH Alone               |
| Reporting group description:<br>Subjects received 45 µg/kg rhGH alone, administered once daily by injection.<br>Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).                            |                                   |
| Reporting group title                                                                                                                                                                                                                                                                  | 45 µg/kg rhGH + 50 µg/kg rhIGF-1  |
| Reporting group description:<br>Subjects received 45 µg/kg rhGH and 50 µg/kg rhIGF-1, administered once daily as separate injections.<br>Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).   |                                   |
| Reporting group title                                                                                                                                                                                                                                                                  | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 |
| Reporting group description:<br>Subjects received 45 µg/kg rhGH and 100 µg/kg rhIGF-1, administered once daily as separate injections.<br>Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).  |                                   |
| Reporting group title                                                                                                                                                                                                                                                                  | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
| Reporting group description:<br>Subjects received 45 µg/kg rhGH and 150 µg/kg rhIGF-1, administered once daily as separate injections.<br>Treatment commenced on Day 1 (Visit 2) at 50% of the assigned doses. Full doses commenced on the day immediately following Day 15 (Visit 3). |                                   |

### Primary: Height Velocity During the First Year of Treatment

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Height Velocity During the First Year of Treatment |
| End point description:<br>Height was measured standing, without shoes, as the average of three measurements (the subject being repositioned each time) by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer which was calibrated prior to measurement of each subject and a calibration log kept. Height was evaluated at each study visit from screening up to the end-of-year-one visit. First-year height velocity (growth in centimeters [cm]) is presented for the Modified Intent-To-Treat (MITT) population, consisting of all subjects who were randomized and had at least one post-baseline height measurement. Missing end-of-year-one height measurements were imputed using the last observation carried forward (LOCF) method. |                                                    |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Primary                                            |
| End point timeframe:<br>Baseline (Day 1) and at Year 1 (Week 52).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                    |

| End point values                     | 45 µg/kg rhGH Alone | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
|--------------------------------------|---------------------|----------------------------------|-----------------------------------|-----------------------------------|
| Subject group type                   | Reporting group     | Reporting group                  | Reporting group                   | Reporting group                   |
| Number of subjects analysed          | 25                  | 27                               | 27                                | 26                                |
| Units: cm/year                       |                     |                                  |                                   |                                   |
| arithmetic mean (standard deviation) | 9.3 (± 1.7)         | 10.1 (± 1.3)                     | 9.7 (± 2.5)                       | 11.2 (± 2.1)                      |

## Statistical analyses

|                                                                                                                                                                                                                                                                                          |                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                        | 45 rhGH + 50 rhIGF-1 vs 45 rhGH Alone                  |
| Statistical analysis description:                                                                                                                                                                                                                                                        |                                                        |
| Comparison of 45 µg/kg rhGH + 50 µg/kg rhIGF-1 combination treatment versus 45 µg/kg rhGH monotherapy using an analysis of covariance (ANCOVA), with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates. |                                                        |
| Comparison groups                                                                                                                                                                                                                                                                        | 45 µg/kg rhGH Alone v 45 µg/kg rhGH + 50 µg/kg rhIGF-1 |
| Number of subjects included in analysis                                                                                                                                                                                                                                                  | 52                                                     |
| Analysis specification                                                                                                                                                                                                                                                                   | Pre-specified                                          |
| Analysis type                                                                                                                                                                                                                                                                            | superiority                                            |
| P-value                                                                                                                                                                                                                                                                                  | = 0.243 <sup>[1]</sup>                                 |
| Method                                                                                                                                                                                                                                                                                   | ANCOVA                                                 |
| Parameter estimate                                                                                                                                                                                                                                                                       | Least squares (LS) mean difference                     |
| Point estimate                                                                                                                                                                                                                                                                           | 0.86                                                   |
| Confidence interval                                                                                                                                                                                                                                                                      |                                                        |
| level                                                                                                                                                                                                                                                                                    | 95 %                                                   |
| sides                                                                                                                                                                                                                                                                                    | 2-sided                                                |
| lower limit                                                                                                                                                                                                                                                                              | -0.18                                                  |
| upper limit                                                                                                                                                                                                                                                                              | 1.91                                                   |

Notes:

[1] - The two-sided p-values for the comparisons are adjusted for multiple comparisons using Dunnett's test.

|                                                                                                                                                                                                                                                               |                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                             | 45 rhGH + 100 rhIGF-1 vs 45 rhGH Alone                  |
| Statistical analysis description:                                                                                                                                                                                                                             |                                                         |
| Comparison of 45 µg/kg rhGH + 100 µg/kg rhIGF-1 combination treatment versus 45 µg/kg rhGH monotherapy using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates. |                                                         |
| Comparison groups                                                                                                                                                                                                                                             | 45 µg/kg rhGH Alone v 45 µg/kg rhGH + 100 µg/kg rhIGF-1 |
| Number of subjects included in analysis                                                                                                                                                                                                                       | 52                                                      |
| Analysis specification                                                                                                                                                                                                                                        | Pre-specified                                           |
| Analysis type                                                                                                                                                                                                                                                 | superiority                                             |
| P-value                                                                                                                                                                                                                                                       | = 0.722 <sup>[2]</sup>                                  |
| Method                                                                                                                                                                                                                                                        | ANCOVA                                                  |
| Parameter estimate                                                                                                                                                                                                                                            | LS mean difference                                      |
| Point estimate                                                                                                                                                                                                                                                | 0.45                                                    |
| Confidence interval                                                                                                                                                                                                                                           |                                                         |
| level                                                                                                                                                                                                                                                         | 95 %                                                    |
| sides                                                                                                                                                                                                                                                         | 2-sided                                                 |
| lower limit                                                                                                                                                                                                                                                   | -0.6                                                    |
| upper limit                                                                                                                                                                                                                                                   | 1.5                                                     |

Notes:

[2] - The two-sided p-values for the comparisons are adjusted for multiple comparisons using Dunnett's test.

|                                   |                                        |
|-----------------------------------|----------------------------------------|
| <b>Statistical analysis title</b> | 45 rhGH + 150 rhIGF-1 vs 45 rhGH Alone |
|-----------------------------------|----------------------------------------|

**Statistical analysis description:**

Comparison of 45 µg/kg rhGH + 150 µg/kg rhIGF-1 combination treatment versus 45 µg/kg rhGH monotherapy using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.

|                                         |                                                         |
|-----------------------------------------|---------------------------------------------------------|
| Comparison groups                       | 45 µg/kg rhGH Alone v 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
| Number of subjects included in analysis | 51                                                      |
| Analysis specification                  | Pre-specified                                           |
| Analysis type                           | superiority                                             |
| P-value                                 | = 0.001 <sup>[3]</sup>                                  |
| Method                                  | ANCOVA                                                  |
| Parameter estimate                      | LS mean difference                                      |
| Point estimate                          | 1.95                                                    |
| Confidence interval                     |                                                         |
| level                                   | 95 %                                                    |
| sides                                   | 2-sided                                                 |
| lower limit                             | 0.9                                                     |
| upper limit                             | 3.01                                                    |

**Notes:**

[3] - The two-sided p-values for the comparisons are adjusted for multiple comparisons using Dunnett's method.

|                                   |                                               |
|-----------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b> | 45 rhGH + 100 rhIGF-1 vs 45 rhGH + 50 rhIGF-1 |
|-----------------------------------|-----------------------------------------------|

**Statistical analysis description:**

Comparison of 45 µg/kg rhGH + 100 µg/kg rhIGF-1 versus 45 µg/kg rhGH + 50 µg/kg rhIGF-1 combination treatments using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.

|                                         |                                                                      |
|-----------------------------------------|----------------------------------------------------------------------|
| Comparison groups                       | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 v 45 µg/kg rhGH + 100 µg/kg rhIGF-1 |
| Number of subjects included in analysis | 54                                                                   |
| Analysis specification                  | Pre-specified                                                        |
| Analysis type                           | superiority                                                          |
| P-value                                 | = 0.427                                                              |
| Method                                  | ANCOVA                                                               |
| Parameter estimate                      | LS mean difference                                                   |
| Point estimate                          | -0.41                                                                |
| Confidence interval                     |                                                                      |
| level                                   | 95 %                                                                 |
| sides                                   | 2-sided                                                              |
| lower limit                             | -1.44                                                                |
| upper limit                             | 0.61                                                                 |

|                                   |                                               |
|-----------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b> | 45 rhGH + 150 rhIGF-1 vs 45 rhGH + 50 rhIGF-1 |
|-----------------------------------|-----------------------------------------------|

**Statistical analysis description:**

Comparison of 45 µg/kg rhGH + 150 µg/kg rhIGF-1 versus 45 µg/kg rhGH + 50 µg/kg rhIGF-1 combination treatments using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.

|                   |                                                                      |
|-------------------|----------------------------------------------------------------------|
| Comparison groups | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 v 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
|-------------------|----------------------------------------------------------------------|

|                                         |                    |
|-----------------------------------------|--------------------|
| Number of subjects included in analysis | 53                 |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | superiority        |
| P-value                                 | = 0.04             |
| Method                                  | ANCOVA             |
| Parameter estimate                      | LS mean difference |
| Point estimate                          | 1.09               |
| Confidence interval                     |                    |
| level                                   | 95 %               |
| sides                                   | 2-sided            |
| lower limit                             | 0.05               |
| upper limit                             | 2.12               |

|                                   |                                                |
|-----------------------------------|------------------------------------------------|
| <b>Statistical analysis title</b> | 45 rhGH + 150 rhIGF-1 vs 45 rhGH + 100 rhIGF-1 |
|-----------------------------------|------------------------------------------------|

Statistical analysis description:

Comparison of 45 µg/kg rhGH + 150 µg/kg rhIGF-1 versus 45 µg/kg rhGH + 100 µg/kg rhIGF-1 combination treatments using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.

|                                         |                                                                       |
|-----------------------------------------|-----------------------------------------------------------------------|
| Comparison groups                       | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 v 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
| Number of subjects included in analysis | 53                                                                    |
| Analysis specification                  | Pre-specified                                                         |
| Analysis type                           | superiority                                                           |
| P-value                                 | = 0.005                                                               |
| Method                                  | ANCOVA                                                                |
| Parameter estimate                      | LS mean difference                                                    |
| Point estimate                          | 1.5                                                                   |
| Confidence interval                     |                                                                       |
| level                                   | 95 %                                                                  |
| sides                                   | 2-sided                                                               |
| lower limit                             | 0.46                                                                  |
| upper limit                             | 2.54                                                                  |

## Secondary: Height Velocity During the Second, Third and Fourth Year of Treatment

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Height Velocity During the Second, Third and Fourth Year of Treatment |
|-----------------|-----------------------------------------------------------------------|

End point description:

Height was measured standing, without shoes, as the average of three measurements (the subject being repositioned each time) by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer which was calibrated prior to measurement of each subject and a calibration log kept. Height was evaluated at each study visit from screening up to end of study. Second, third and fourth-year height velocity (growth in cm) is presented for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement. Missing end-of-year height measurements were imputed for Years 2, 3 and 4 only if a subject had at least one height value recorded in the specified year (imputation by LOCF method).

n = number of subjects with data available for analysis for each indicated timepoint.

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

End point timeframe:

Baseline (Day 1) and at Years 2, 3 and 4 (Weeks 104, 156 and 208, respectively).

| End point values                     | 45 µg/kg rhGH Alone | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
|--------------------------------------|---------------------|----------------------------------|-----------------------------------|-----------------------------------|
| Subject group type                   | Reporting group     | Reporting group                  | Reporting group                   | Reporting group                   |
| Number of subjects analysed          | 25                  | 27                               | 27                                | 26                                |
| Units: cm/year                       |                     |                                  |                                   |                                   |
| arithmetic mean (standard deviation) |                     |                                  |                                   |                                   |
| Year 2 (n=24,25,22,24)               | 8.4 (± 1.3)         | 9.1 (± 1.2)                      | 9.4 (± 1.6)                       | 10.1 (± 1.8)                      |
| Year 3 (n=22,22,20,22)               | 8.0 (± 1.1)         | 8.4 (± 1.0)                      | 8.9 (± 1.3)                       | 9.2 (± 1.5)                       |
| Year 4 (n=17,16,15,16)               | 7.7 (± 0.9)         | 8.1 (± 0.8)                      | 8.4 (± 1.2)                       | 8.3 (± 1.3)                       |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cumulative Change in Height SDS During the First, Second, Third and Fourth Year of Treatment

|                 |                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------|
| End point title | Cumulative Change in Height SDS During the First, Second, Third and Fourth Year of Treatment |
|-----------------|----------------------------------------------------------------------------------------------|

End point description:

Height was measured standing, without shoes, as the average of three measurements (the subject being repositioned each time) by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer which was calibrated prior to measurement of each subject and a calibration log kept. Height was evaluated at each study visit from screening up to end of study. Height SDS was calculated using the National Center for Health Statistics 2000 data as provided by the Center for Disease Control. Mean change from baseline in height SDS at Years 1, 2, 3 and 4 is presented for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement. Missing end-of-year-one height SDS was imputed using last LOCF method; height SDS was imputed for Years 2, 3 and 4 only if a subject had at least one height value recorded in the specified year.

n = number of subjects with data available for analysis for each indicated timepoint.

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

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

| End point values                     | 45 µg/kg rhGH Alone | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
|--------------------------------------|---------------------|----------------------------------|-----------------------------------|-----------------------------------|
| Subject group type                   | Reporting group     | Reporting group                  | Reporting group                   | Reporting group                   |
| Number of subjects analysed          | 25                  | 27                               | 27                                | 26                                |
| Units: SDS                           |                     |                                  |                                   |                                   |
| arithmetic mean (standard deviation) |                     |                                  |                                   |                                   |
| Year 1 (n=25,27,27,26)               | 0.7 (± 0.3)         | 0.9 (± 0.2)                      | 0.8 (± 0.4)                       | 1.0 (± 0.4)                       |
| Year 2 (n=24,25,22,24)               | 1.0 (± 0.4)         | 1.4 (± 0.4)                      | 1.4 (± 0.5)                       | 1.6 (± 0.6)                       |
| Year 3 (n=22,22,20,22)               | 1.3 (± 0.5)         | 1.6 (± 0.4)                      | 1.8 (± 0.7)                       | 1.9 (± 0.6)                       |
| Year 4 (n=17,16,15,16)               | 1.5 (± 0.5)         | 1.8 (± 0.5)                      | 2.1 (± 0.8)                       | 2.0 (± 0.7)                       |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Predicted Adult Height (PAH) at Years 1, 2, 3 and 4

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | Predicted Adult Height (PAH) at Years 1, 2, 3 and 4 |
|-----------------|-----------------------------------------------------|

End point description:

PAH was calculated by the Roche-Wainer-Thissen (RWT) method, as refined by Khamis and Guo and adjusted for growth after age 18 according to Roche and Davila, and was summarized for subjects completing the year in the context of baseline height SDS and mid-parental target height SDS. The mid-parental target height SDS was defined as:

$0.4 * (\text{Mother's height SDS} + \text{Father's height SDS})$ .

RWT PAH SDS at baseline (Day 1) and at Years 1, 2, 3 and 4, as well as mid-parental target height SDS, are presented for the completer population, consisting of all subjects that remained in the study until a specific time point (ie, Year 1, Year 2, Year 3 and Year 4).

n = number of subjects with data available for analysis for each indicated timepoint.

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

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

| End point values                              | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH<br>+ 50 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 100 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 150 µg/kg<br>rhIGF-1 |
|-----------------------------------------------|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| Subject group type                            | Reporting group        | Reporting group                        | Reporting group                         | Reporting group                         |
| Number of subjects analysed                   | 25                     | 27                                     | 27                                      | 26                                      |
| Units: SDS                                    |                        |                                        |                                         |                                         |
| arithmetic mean (standard deviation)          |                        |                                        |                                         |                                         |
| Baseline (n=25,27,27,26)                      | -1.67 (± 0.51)         | -1.83 (± 0.58)                         | -1.69 (± 0.59)                          | -1.76 (± 0.73)                          |
| Year 1 (n=24,25,22,25)                        | -1.12 (± 0.57)         | -1.22 (± 0.58)                         | -0.99 (± 0.55)                          | -1.01 (± 0.80)                          |
| Year 2 (n=22,21,20,22)                        | -0.96 (± 0.56)         | -0.81 (± 0.55)                         | -0.66 (± 0.56)                          | -0.69 (± 0.91)                          |
| Year 3 (n=21,19,19,20)                        | -0.78 (± 0.63)         | -0.65 (± 0.60)                         | -0.42 (± 0.62)                          | -0.64 (± 0.98)                          |
| Year 4 (n=3,4,4,3)                            | -1.22 (± 0.59)         | -0.44 (± 0.81)                         | 0.49 (± 0.60)                           | -0.07 (± 0.89)                          |
| Mid-parental target height<br>(n=25,27,27,26) | -0.51 (± 0.38)         | -0.64 (± 0.52)                         | -0.53 (± 0.50)                          | -0.47 (± 0.51)                          |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total Change from Baseline in Body Mass Index (BMI) SDS at Years 1, 2, 3, 4 and End of Study

|                 |                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------|
| End point title | Total Change from Baseline in Body Mass Index (BMI) SDS at Years 1, 2, 3, 4 and End of Study |
|-----------------|----------------------------------------------------------------------------------------------|

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**End point description:**

Weight in kilograms (kg) was recorded from a single observation of the subject in light clothing or dressing gown with shoes removed. BMI was calculated by weight divided by height squared and measured as kg per square meter (kg/m<sup>2</sup>). Height and weight were evaluated at each study visit from screening up to the end of study. Mean change from baseline in BMI SDS at Years 1, 2, 3 and 4, and at end of study is presented for the completer population, consisting of all subjects that remained in the study until a specific time point (ie, Year 1, Year 2, Year 3 and Year 4).

n = number of subjects with data available for analysis for each indicated timepoint.

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

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**End point timeframe:**

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

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| End point values                          | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH<br>+ 50 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 100 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 150 µg/kg<br>rhIGF-1 |
|-------------------------------------------|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| Subject group type                        | Reporting group        | Reporting group                        | Reporting group                         | Reporting group                         |
| Number of subjects analysed               | 25                     | 27                                     | 27                                      | 26                                      |
| Units: SDS                                |                        |                                        |                                         |                                         |
| arithmetic mean (standard deviation)      |                        |                                        |                                         |                                         |
| Change to Year 1 (n=24,25,22,25)          | 0.24 (± 0.43)          | 0.31 (± 0.39)                          | 0.36 (± 0.41)                           | 0.54 (± 0.40)                           |
| Change to Year 2 (n=22,21,20,22)          | 0.31 (± 0.49)          | 0.57 (± 0.41)                          | 0.49 (± 0.44)                           | 0.59 (± 0.46)                           |
| Change to Year 3 (n=21,19,19,20)          | 0.35 (± 0.58)          | 0.62 (± 0.43)                          | 0.49 (± 0.59)                           | 0.71 (± 0.54)                           |
| Change to Year 4 (n=3,5,5,4)              | 0.27 (± 0.52)          | 0.64 (± 0.58)                          | 0.65 (± 0.90)                           | 1.20 (± 0.91)                           |
| Change to End of Study<br>(n=25,27,27,26) | 0.34 (± 0.54)          | 0.45 (± 0.45)                          | 0.42 (± 0.53)                           | 0.64 (± 0.60)                           |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Skeletal Maturation (Bone Age) at Years 1, 2, 3 and 4**

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|                 |                                                       |
|-----------------|-------------------------------------------------------|
| End point title | Skeletal Maturation (Bone Age) at Years 1, 2, 3 and 4 |
|-----------------|-------------------------------------------------------|

---

**End point description:**

Plain X-rays of the left hand and wrist exposed for bone age appraisal were sent to a central facility for standardized evaluation. Bone age was evaluated at screening and each end-of-year visit up to the end of study. Bone age is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the completer population, consisting of all subjects that remained in the study until a specific time point (ie, Year 1, Year 2, Year 3 and Year 4).

n = number of subjects with data available for analysis for each indicated timepoint.

---

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

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**End point timeframe:**

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

---

| End point values                     | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH<br>+ 50 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 100 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 150 µg/kg<br>rhIGF-1 |
|--------------------------------------|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| Subject group type                   | Reporting group        | Reporting group                        | Reporting group                         | Reporting group                         |
| Number of subjects analysed          | 25                     | 27                                     | 27                                      | 26                                      |
| Units: years                         |                        |                                        |                                         |                                         |
| arithmetic mean (standard deviation) |                        |                                        |                                         |                                         |
| Baseline (n=25,27,27,26)             | 7.6 (± 1.8)            | 7.3 (± 1.9)                            | 7.2 (± 2.0)                             | 7.4 (± 2.0)                             |
| Year 1 (n=24,25,22,25)               | 9.0 (± 1.9)            | 8.5 (± 1.9)                            | 8.4 (± 2.2)                             | 8.5 (± 2.1)                             |
| Year 2 (n= 22,21,20,22)              | 10.3 (± 2.0)           | 9.6 (± 2.1)                            | 9.8 (± 2.4)                             | 9.9 (± 2.2)                             |
| Year 3 (n=21,19,19,20)               | 11.4 (± 2.0)           | 10.9 (± 2.2)                           | 11.4 (± 2.4)                            | 10.9 (± 2.2)                            |
| Year 4 (n=3,4,5,3)                   | 12.4 (± 1.0)           | 10.9 (± 1.8)                           | 12.2 (± 3.0)                            | 12.5 (± 2.1)                            |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentration of GH at Years 1, 2, 3 and 4

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Serum Concentration of GH at Years 1, 2, 3 and 4 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                  |
| Growth factor panels for measuring GH were evaluated at each study visit from screening up to the end-of-year-four visit. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for GH is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.<br>n = number of subjects with data available for analysis for each indicated timepoint. |                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Secondary                                        |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                  |
| Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                  |

| End point values                        | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH<br>+ 50 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 100 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 150 µg/kg<br>rhIGF-1 |
|-----------------------------------------|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| Subject group type                      | Reporting group        | Reporting group                        | Reporting group                         | Reporting group                         |
| Number of subjects analysed             | 25                     | 27                                     | 27                                      | 26                                      |
| Units: nanograms per milliliter (ng/mL) |                        |                                        |                                         |                                         |
| arithmetic mean (standard deviation)    |                        |                                        |                                         |                                         |
| Baseline (n=23,25,18,25)                | 1.1 (± 2.2)            | 2.9 (± 8.1)                            | 2.4 (± 4.5)                             | 1.9 (± 2.3)                             |
| Year 1 (Trough) (n=23,25,18,25)         | 1.7 (± 2.1)            | 3.5 (± 12.9)                           | 2.1 (± 3.2)                             | 1.4 (± 2.1)                             |
| Year 2 (Trough) (n=21,20,16,20)         | 4.0 (± 6.0)            | 2.2 (± 4.2)                            | 2.7 (± 3.9)                             | 1.4 (± 1.2)                             |
| Year 3 (Trough) (n=20,18,15,20)         | 2.8 (± 5.1)            | 1.3 (± 1.6)                            | 1.5 (± 1.4)                             | 1.9 (± 3.5)                             |
| Year 4 (Trough) (n=3,5,4,3)             | 1.2 (± 0.3)            | 0.5 (± 0.4)                            | 3.0 (± 2.9)                             | 1.1 (± 0.6)                             |

## Statistical analyses

No statistical analyses for this end point



**Secondary: Serum Concentration of IGF-1 at Years 1, 2, 3 and 4**

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | Serum Concentration of IGF-1 at Years 1, 2, 3 and 4 |
|-----------------|-----------------------------------------------------|

End point description:

Growth factor panels for measuring IGF-1 were evaluated at each study visit from screening up to the end of study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for IGF-1 is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

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

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

| End point values                     | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH<br>+ 50 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 100 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 150 µg/kg<br>rhIGF-1 |
|--------------------------------------|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| Subject group type                   | Reporting group        | Reporting group                        | Reporting group                         | Reporting group                         |
| Number of subjects analysed          | 25                     | 27                                     | 27                                      | 26                                      |
| Units: ng/mL                         |                        |                                        |                                         |                                         |
| arithmetic mean (standard deviation) |                        |                                        |                                         |                                         |
| Baseline (n=24,25,22,25)             | 108.3 (± 39.8)         | 87.1 (± 31.0)                          | 100.2 (± 41.4)                          | 96.7 (± 38.8)                           |
| Year 1 (Trough) (n=24,25,22,25)      | 278.2 (± 95.5)         | 326.9 (± 108.9)                        | 397.8 (± 185.4)                         | 296.0 (± 126.8)                         |
| Year 2 (Trough) (n=22,21,20,22)      | 312.8 (± 97.2)         | 427.2 (± 178.5)                        | 539.3 (± 195.9)                         | 466.4 (± 178.6)                         |
| Year 3 (Trough) (n=21,19,19,20)      | 335.3 (± 110.0)        | 404.9 (± 140.4)                        | 462.2 (± 156.4)                         | 441.3 (± 226.0)                         |
| Year 4 (Trough) (n=3,5,5,3)          | 347.7 (± 130.7)        | 363.6 (± 125.4)                        | 546.2 (± 265.8)                         | 607.7 (± 65.0)                          |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Serum Concentration of Insulin-Like Growth Factor Binding Protein-1 (IGFBP-1) at Years 1, 2, 3 and 4**

|                 |                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------|
| End point title | Serum Concentration of Insulin-Like Growth Factor Binding Protein-1 (IGFBP-1) at Years 1, 2, 3 and 4 |
|-----------------|------------------------------------------------------------------------------------------------------|

End point description:

Growth factor panels for measuring IGFBP-1 were evaluated at baseline and various visits during the study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for IGFBP-1 is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

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

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

| End point values                     | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH<br>+ 50 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 100 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 150 µg/kg<br>rhIGF-1 |
|--------------------------------------|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| Subject group type                   | Reporting group        | Reporting group                        | Reporting group                         | Reporting group                         |
| Number of subjects analysed          | 25                     | 27                                     | 27                                      | 26                                      |
| Units: ng/mL                         |                        |                                        |                                         |                                         |
| arithmetic mean (standard deviation) |                        |                                        |                                         |                                         |
| Baseline (n=24,24,21,24)             | 87.8 (± 54.5)          | 102.5 (± 37.2)                         | 95.7 (± 50.0)                           | 122.4 (± 53.7)                          |
| Year 1 (Trough) (n=24,24,21,24)      | 45.7 (± 38.0)          | 63.8 (± 50.1)                          | 68.2 (± 61.6)                           | 88.8 (± 47.4)                           |
| Year 2 (Trough) (n=22,21,19,20)      | 59.4 (± 45.6)          | 58.2 (± 47.7)                          | 53.3 (± 35.3)                           | 71.7 (± 46.1)                           |
| Year 3 (Trough) (n=21,19,18,19)      | 46.1 (± 35.2)          | 60.4 (± 52.5)                          | 53.2 (± 34.8)                           | 84.7 (± 53.5)                           |
| Year 4 (Trough) (n=3,5,5,3)          | 100.0 (± 60.4)         | 46.8 (± 58.0)                          | 49.2 (± 20.7)                           | 49.0 (± 26.9)                           |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentration of Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3) at Years 1, 2, 3 and 4

|                 |                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------|
| End point title | Serum Concentration of Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3) at Years 1, 2, 3 and 4 |
|-----------------|------------------------------------------------------------------------------------------------------|

End point description:

Growth factor panels for measuring IGFBP-3 were evaluated at each study visit from screening up to the end of study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for IGFBP-3 is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

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

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

| End point values                     | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH<br>+ 50 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 100 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 150 µg/kg<br>rhIGF-1 |
|--------------------------------------|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| Subject group type                   | Reporting group        | Reporting group                        | Reporting group                         | Reporting group                         |
| Number of subjects analysed          | 25                     | 27                                     | 27                                      | 26                                      |
| Units: ng/mL                         |                        |                                        |                                         |                                         |
| arithmetic mean (standard deviation) |                        |                                        |                                         |                                         |
| Baseline (n=24,25,22,25)             | 2204.2 (± 387.3)       | 2160.0 (± 421.3)                       | 2113.6 (± 486.3)                        | 2196.0 (± 612.0)                        |
| Year 1 (Trough) (n=24,25,22,25)      | 2954.2 (± 618.5)       | 2784.0 (± 755.9)                       | 2677.3 (± 548.5)                        | 2624.0 (± 598.8)                        |
| Year 2 (Trough) (n=22,21,20,22)      | 2813.6 (± 399.2)       | 2942.9 (± 552.8)                       | 3060.0 (± 703.7)                        | 2754.5 (± 600.6)                        |
| Year 3 (Trough) (n=21,19,19,20)      | 3404.8 (± 476.9)       | 3431.6 (± 718.1)                       | 3373.7 (± 479.4)                        | 3260.0 (± 908.1)                        |

|                             |                  |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|------------------|
| Year 4 (Trough) (n=3,5,5,3) | 3733.3 (± 378.6) | 3260.0 (± 709.2) | 3620.0 (± 957.6) | 3466.7 (± 461.9) |
|-----------------------------|------------------|------------------|------------------|------------------|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentration of Acid-Labile Subunit (ALS) at Years 1, 2, 3 and 4

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Serum Concentration of Acid-Labile Subunit (ALS) at Years 1, 2, 3 and 4 |
|-----------------|-------------------------------------------------------------------------|

End point description:

Growth factor panels for measuring ALS were evaluated at baseline and various visits during the study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for ALS is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

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

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

| End point values                     | 45 µg/kg rhGH Alone | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
|--------------------------------------|---------------------|----------------------------------|-----------------------------------|-----------------------------------|
| Subject group type                   | Reporting group     | Reporting group                  | Reporting group                   | Reporting group                   |
| Number of subjects analysed          | 25                  | 27                               | 27                                | 26                                |
| Units: milligrams per liter          |                     |                                  |                                   |                                   |
| arithmetic mean (standard deviation) |                     |                                  |                                   |                                   |
| Baseline (n=25,26,26,25)             | 10.6 (± 3.0)        | 10.0 (± 3.4)                     | 10.9 (± 3.0)                      | 11.0 (± 4.1)                      |
| Year 1 (Trough) (n=24,24,21,24)      | 16.0 (± 4.0)        | 12.7 (± 2.3)                     | 14.0 (± 3.9)                      | 11.5 (± 2.8)                      |
| Year 2 (Trough) (n=22,21,19,20)      | 15.2 (± 4.3)        | 14.3 (± 5.2)                     | 15.7 (± 4.0)                      | 13.7 (± 4.5)                      |
| Year 3 (Trough) (n=21,18,18,19)      | 13.7 (± 2.3)        | 13.0 (± 3.2)                     | 12.9 (± 2.7)                      | 11.2 (± 4.0)                      |
| Year 4 (Trough) (n=3,5,5,3)          | 13.7 (± 1.5)        | 12.0 (± 2.2)                     | 12.0 (± 3.0)                      | 13.7 (± 2.1)                      |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentration of Growth Hormone Binding Protein (GHBP) at Years 1, 2, 3 and 4

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Serum Concentration of Growth Hormone Binding Protein (GHBP) at Years 1, 2, 3 and 4 |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

Growth factor panels for measuring GHBP were evaluated at baseline and various visits during the study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for GHBP is presented at baseline (Day 1) and at Years 1, 2, 3

and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

|                                                                                         |           |
|-----------------------------------------------------------------------------------------|-----------|
| End point type                                                                          | Secondary |
| End point timeframe:                                                                    |           |
| Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively). |           |

| End point values                     | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH<br>+ 50 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 100 µg/kg<br>rhIGF-1 | 45 µg/kg rhGH<br>+ 150 µg/kg<br>rhIGF-1 |
|--------------------------------------|------------------------|----------------------------------------|-----------------------------------------|-----------------------------------------|
| Subject group type                   | Reporting group        | Reporting group                        | Reporting group                         | Reporting group                         |
| Number of subjects analysed          | 25                     | 27                                     | 27                                      | 26                                      |
| Units: picomoles per liter           |                        |                                        |                                         |                                         |
| arithmetic mean (standard deviation) |                        |                                        |                                         |                                         |
| Baseline (n=25,26,25,25)             | 785.8 (±<br>291.1)     | 735.8 (±<br>343.5)                     | 698.8 (±<br>212.2)                      | 719.0 (±<br>261.5)                      |
| Year 1 (Trough) (n=23,24,20,24)      | 729.4 (±<br>229.5)     | 576.9 (±<br>211.0)                     | 598.9 (±<br>187.3)                      | 530.5 (±<br>233.5)                      |
| Year 2 (Trough) (n=22,21,18,21)      | 725.6 (±<br>308.4)     | 589.3 (±<br>171.6)                     | 562.5 (±<br>184.4)                      | 564.6 (±<br>171.9)                      |
| Year 3 (Trough) (n=21,17,17,19)      | 672.0 (±<br>224.4)     | 646.9 (±<br>204.1)                     | 614.3 (±<br>210.9)                      | 554.9 (±<br>197.0)                      |
| Year 4 (Trough) (n=3,5,5,3)          | 714.0 (± 38.5)         | 516.9 (±<br>252.5)                     | 798.2 (±<br>336.1)                      | 519.7 (±<br>141.1)                      |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected from randomization (Day 1) until 30 days after the subject was terminated from the study. Overall timeframe up to a maximum of approximately 4 years.

Adverse event reporting additional description:

Safety population consisted of all subjects who were randomized.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | 45 µg/kg rhGH Alone |
|-----------------------|---------------------|

Reporting group description:

Subjects received 45 µg/kg rhGH alone, administered once daily by injection.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 |
|-----------------------|----------------------------------|

Reporting group description:

Subjects received 45 µg/kg rhGH and 50 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects received 45 µg/kg rhGH and 100 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | 45 µg/kg rhGH + 150 µg/kg rhIGF-1 |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects received 45 µg/kg rhGH and 150 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned doses. Full doses commenced on the day immediately following Day 15 (Visit 3).

| Serious adverse events                            | 45 µg/kg rhGH Alone | 45 µg/kg rhGH + 50 µg/kg rhIGF-1 | 45 µg/kg rhGH + 100 µg/kg rhIGF-1 |
|---------------------------------------------------|---------------------|----------------------------------|-----------------------------------|
| Total subjects affected by serious adverse events |                     |                                  |                                   |
| subjects affected / exposed                       | 1 / 26 (3.85%)      | 1 / 27 (3.70%)                   | 2 / 27 (7.41%)                    |
| number of deaths (all causes)                     | 0                   | 0                                | 0                                 |
| number of deaths resulting from adverse events    | 0                   | 0                                | 0                                 |
| Injury, poisoning and procedural complications    |                     |                                  |                                   |
| Forearm fracture                                  |                     |                                  |                                   |
| subjects affected / exposed                       | 0 / 26 (0.00%)      | 0 / 27 (0.00%)                   | 1 / 27 (3.70%)                    |
| occurrences causally related to treatment / all   | 0 / 0               | 0 / 0                            | 0 / 1                             |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0                            | 0 / 0                             |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Nervous system disorders                        |                |                |                |
| Intracranial pressure increased                 |                |                |                |
| subjects affected / exposed                     | 0 / 26 (0.00%) | 0 / 27 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Thrombocytopenia                                |                |                |                |
| subjects affected / exposed                     | 0 / 26 (0.00%) | 1 / 27 (3.70%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Evans syndrome                                  |                |                |                |
| subjects affected / exposed                     | 0 / 26 (0.00%) | 1 / 27 (3.70%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Papilloedema                                    |                |                |                |
| subjects affected / exposed                     | 0 / 26 (0.00%) | 0 / 27 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Haematuria                                      |                |                |                |
| subjects affected / exposed                     | 0 / 26 (0.00%) | 1 / 27 (3.70%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Viral infection                                 |                |                |                |
| subjects affected / exposed                     | 0 / 26 (0.00%) | 1 / 27 (3.70%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis viral                           |                |                |                |
| subjects affected / exposed                     | 1 / 26 (3.85%) | 0 / 27 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                    |                                      |  |  |
|------------------------------------|--------------------------------------|--|--|
| <b>Serious adverse events</b>      | 45 µg/kg rhGH +<br>150 µg/kg rhIGF-1 |  |  |
| Total subjects affected by serious |                                      |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| adverse events                                  |                |  |  |
| subjects affected / exposed                     | 1 / 26 (3.85%) |  |  |
| number of deaths (all causes)                   | 0              |  |  |
| number of deaths resulting from adverse events  | 0              |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Forearm fracture                                |                |  |  |
| subjects affected / exposed                     | 0 / 26 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Intracranial pressure increased                 |                |  |  |
| subjects affected / exposed                     | 0 / 26 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Thrombocytopenia                                |                |  |  |
| subjects affected / exposed                     | 0 / 26 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Evans syndrome                                  |                |  |  |
| subjects affected / exposed                     | 0 / 26 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Papilloedema                                    |                |  |  |
| subjects affected / exposed                     | 1 / 26 (3.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Haematuria                                      |                |  |  |
| subjects affected / exposed                     | 0 / 26 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Viral infection                                 |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 0 / 26 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis viral                           |                |  |  |
| subjects affected / exposed                     | 0 / 26 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                                   | 45 µg/kg rhGH<br>Alone | 45 µg/kg rhGH + 50<br>µg/kg rhIGF-1 | 45 µg/kg rhGH +<br>100 µg/kg rhIGF-1 |
|---------------------------------------------------------------------|------------------------|-------------------------------------|--------------------------------------|
| Total subjects affected by non-serious adverse events               |                        |                                     |                                      |
| subjects affected / exposed                                         | 26 / 26 (100.00%)      | 27 / 27 (100.00%)                   | 27 / 27 (100.00%)                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                                     |                                      |
| Skin papilloma                                                      |                        |                                     |                                      |
| subjects affected / exposed                                         | 2 / 26 (7.69%)         | 0 / 27 (0.00%)                      | 2 / 27 (7.41%)                       |
| occurrences (all)                                                   | 2                      | 0                                   | 3                                    |
| General disorders and administration site conditions                |                        |                                     |                                      |
| Pyrexia                                                             |                        |                                     |                                      |
| subjects affected / exposed                                         | 9 / 26 (34.62%)        | 15 / 27 (55.56%)                    | 4 / 27 (14.81%)                      |
| occurrences (all)                                                   | 17                     | 27                                  | 22                                   |
| Injection site pain                                                 |                        |                                     |                                      |
| subjects affected / exposed                                         | 4 / 26 (15.38%)        | 1 / 27 (3.70%)                      | 0 / 27 (0.00%)                       |
| occurrences (all)                                                   | 4                      | 2                                   | 0                                    |
| Malaise                                                             |                        |                                     |                                      |
| subjects affected / exposed                                         | 1 / 26 (3.85%)         | 0 / 27 (0.00%)                      | 2 / 27 (7.41%)                       |
| occurrences (all)                                                   | 1                      | 0                                   | 2                                    |
| Injection site bruising                                             |                        |                                     |                                      |
| subjects affected / exposed                                         | 4 / 26 (15.38%)        | 4 / 27 (14.81%)                     | 4 / 27 (14.81%)                      |
| occurrences (all)                                                   | 4                      | 5                                   | 4                                    |
| Injection site hypertrophy                                          |                        |                                     |                                      |
| subjects affected / exposed                                         | 0 / 26 (0.00%)         | 6 / 27 (22.22%)                     | 7 / 27 (25.93%)                      |
| occurrences (all)                                                   | 0                      | 8                                   | 13                                   |
| Injection site induration                                           |                        |                                     |                                      |



|                                                 |                 |                  |                 |
|-------------------------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 26 (0.00%)  | 1 / 27 (3.70%)   | 2 / 27 (7.41%)  |
| occurrences (all)                               | 0               | 1                | 2               |
| Influenza like illness                          |                 |                  |                 |
| subjects affected / exposed                     | 1 / 26 (3.85%)  | 0 / 27 (0.00%)   | 0 / 27 (0.00%)  |
| occurrences (all)                               | 2               | 0                | 0               |
| Injection site erythema                         |                 |                  |                 |
| subjects affected / exposed                     | 0 / 26 (0.00%)  | 2 / 27 (7.41%)   | 0 / 27 (0.00%)  |
| occurrences (all)                               | 0               | 2                | 0               |
| Injection site urticaria                        |                 |                  |                 |
| subjects affected / exposed                     | 2 / 26 (7.69%)  | 3 / 27 (11.11%)  | 1 / 27 (3.70%)  |
| occurrences (all)                               | 3               | 3                | 2               |
| Fatigue                                         |                 |                  |                 |
| subjects affected / exposed                     | 1 / 26 (3.85%)  | 3 / 27 (11.11%)  | 0 / 27 (0.00%)  |
| occurrences (all)                               | 1               | 3                | 0               |
| Feeling hot                                     |                 |                  |                 |
| subjects affected / exposed                     | 0 / 26 (0.00%)  | 2 / 27 (7.41%)   | 0 / 27 (0.00%)  |
| occurrences (all)                               | 0               | 2                | 0               |
| Immune system disorders                         |                 |                  |                 |
| Hypersensitivity                                |                 |                  |                 |
| subjects affected / exposed                     | 1 / 26 (3.85%)  | 1 / 27 (3.70%)   | 0 / 27 (0.00%)  |
| occurrences (all)                               | 1               | 1                | 0               |
| Seasonal allergy                                |                 |                  |                 |
| subjects affected / exposed                     | 2 / 26 (7.69%)  | 3 / 27 (11.11%)  | 3 / 27 (11.11%) |
| occurrences (all)                               | 2               | 4                | 3               |
| Reproductive system and breast disorders        |                 |                  |                 |
| Gynaecomastia                                   |                 |                  |                 |
| subjects affected / exposed                     | 1 / 26 (3.85%)  | 0 / 27 (0.00%)   | 2 / 27 (7.41%)  |
| occurrences (all)                               | 1               | 0                | 2               |
| Respiratory, thoracic and mediastinal disorders |                 |                  |                 |
| Cough                                           |                 |                  |                 |
| subjects affected / exposed                     | 6 / 26 (23.08%) | 14 / 27 (51.85%) | 9 / 27 (33.33%) |
| occurrences (all)                               | 7               | 18               | 16              |
| Pharyngolaryngeal pain                          |                 |                  |                 |
| subjects affected / exposed                     | 3 / 26 (11.54%) | 7 / 27 (25.93%)  | 7 / 27 (25.93%) |
| occurrences (all)                               | 3               | 11               | 10              |
| Nasal congestion                                |                 |                  |                 |

|                                          |                 |                |                 |
|------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed              | 2 / 26 (7.69%)  | 2 / 27 (7.41%) | 3 / 27 (11.11%) |
| occurrences (all)                        | 2               | 2              | 6               |
| Asthma                                   |                 |                |                 |
| subjects affected / exposed              | 0 / 26 (0.00%)  | 1 / 27 (3.70%) | 3 / 27 (11.11%) |
| occurrences (all)                        | 0               | 1              | 4               |
| Epistaxis                                |                 |                |                 |
| subjects affected / exposed              | 2 / 26 (7.69%)  | 0 / 27 (0.00%) | 1 / 27 (3.70%)  |
| occurrences (all)                        | 5               | 0              | 1               |
| Rhinitis allergic                        |                 |                |                 |
| subjects affected / exposed              | 3 / 26 (11.54%) | 2 / 27 (7.41%) | 1 / 27 (3.70%)  |
| occurrences (all)                        | 3               | 2              | 1               |
| Rhinorrhoea                              |                 |                |                 |
| subjects affected / exposed              | 0 / 26 (0.00%)  | 1 / 27 (3.70%) | 2 / 27 (7.41%)  |
| occurrences (all)                        | 0               | 1              | 2               |
| Tonsillar hypertrophy                    |                 |                |                 |
| subjects affected / exposed              | 2 / 26 (7.69%)  | 2 / 27 (7.41%) | 1 / 27 (3.70%)  |
| occurrences (all)                        | 2               | 2              | 1               |
| Adenoidal hypertrophy                    |                 |                |                 |
| subjects affected / exposed              | 2 / 26 (7.69%)  | 1 / 27 (3.70%) | 0 / 27 (0.00%)  |
| occurrences (all)                        | 2               | 1              | 0               |
| Psychiatric disorders                    |                 |                |                 |
| Anxiety                                  |                 |                |                 |
| subjects affected / exposed              | 1 / 26 (3.85%)  | 0 / 27 (0.00%) | 1 / 27 (3.70%)  |
| occurrences (all)                        | 1               | 0              | 1               |
| Attention deficit/hyperactivity disorder |                 |                |                 |
| subjects affected / exposed              | 0 / 26 (0.00%)  | 0 / 27 (0.00%) | 2 / 27 (7.41%)  |
| occurrences (all)                        | 0               | 0              | 2               |
| Attention                                |                 |                |                 |
| subjects affected / exposed              | 0 / 26 (0.00%)  | 0 / 27 (0.00%) | 2 / 27 (7.41%)  |
| occurrences (all)                        | 0               | 0              | 2               |
| Investigations                           |                 |                |                 |
| Insulin-like growth factor increased     |                 |                |                 |
| subjects affected / exposed              | 0 / 26 (0.00%)  | 0 / 27 (0.00%) | 1 / 27 (3.70%)  |
| occurrences (all)                        | 0               | 0              | 1               |
| Body temperature increased               |                 |                |                 |

|                                                                              |                     |                      |                      |
|------------------------------------------------------------------------------|---------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                             | 1 / 26 (3.85%)<br>1 | 3 / 27 (11.11%)<br>4 | 3 / 27 (11.11%)<br>3 |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 26 (3.85%)<br>1 | 2 / 27 (7.41%)<br>2  | 0 / 27 (0.00%)<br>0  |
| Thyroxine free decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 26 (0.00%)<br>0 | 0 / 27 (0.00%)<br>0  | 2 / 27 (7.41%)<br>2  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)         | 2 / 26 (7.69%)<br>2 | 0 / 27 (0.00%)<br>0  | 0 / 27 (0.00%)<br>0  |
| Injury, poisoning and procedural complications                               |                     |                      |                      |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)          | 1 / 26 (3.85%)<br>1 | 0 / 27 (0.00%)<br>0  | 1 / 27 (3.70%)<br>1  |
| Arthropod sting<br>subjects affected / exposed<br>occurrences (all)          | 0 / 26 (0.00%)<br>0 | 0 / 27 (0.00%)<br>0  | 0 / 27 (0.00%)<br>0  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                | 2 / 26 (7.69%)<br>3 | 1 / 27 (3.70%)<br>2  | 0 / 27 (0.00%)<br>0  |
| Skin laceration<br>subjects affected / exposed<br>occurrences (all)          | 2 / 26 (7.69%)<br>2 | 2 / 27 (7.41%)<br>2  | 0 / 27 (0.00%)<br>0  |
| Upper limb fracture<br>subjects affected / exposed<br>occurrences (all)      | 2 / 26 (7.69%)<br>2 | 0 / 27 (0.00%)<br>0  | 1 / 27 (3.70%)<br>1  |
| Concussion<br>subjects affected / exposed<br>occurrences (all)               | 2 / 26 (7.69%)<br>2 | 0 / 27 (0.00%)<br>0  | 0 / 27 (0.00%)<br>0  |
| Joint sprain<br>subjects affected / exposed<br>occurrences (all)             | 1 / 26 (3.85%)<br>1 | 2 / 27 (7.41%)<br>2  | 3 / 27 (11.11%)<br>4 |
| Limb injury                                                                  |                     |                      |                      |

|                                      |                  |                  |                  |
|--------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed          | 0 / 26 (0.00%)   | 2 / 27 (7.41%)   | 0 / 27 (0.00%)   |
| occurrences (all)                    | 0                | 2                | 0                |
| Orthodontic appliance complication   |                  |                  |                  |
| subjects affected / exposed          | 0 / 26 (0.00%)   | 0 / 27 (0.00%)   | 2 / 27 (7.41%)   |
| occurrences (all)                    | 0                | 0                | 2                |
| Cardiac disorders                    |                  |                  |                  |
| Tachycardia                          |                  |                  |                  |
| subjects affected / exposed          | 0 / 26 (0.00%)   | 0 / 27 (0.00%)   | 1 / 27 (3.70%)   |
| occurrences (all)                    | 0                | 0                | 1                |
| Nervous system disorders             |                  |                  |                  |
| Headache                             |                  |                  |                  |
| subjects affected / exposed          | 14 / 26 (53.85%) | 14 / 27 (51.85%) | 17 / 27 (62.96%) |
| occurrences (all)                    | 40               | 43               | 39               |
| Dizziness                            |                  |                  |                  |
| subjects affected / exposed          | 1 / 26 (3.85%)   | 2 / 27 (7.41%)   | 0 / 27 (0.00%)   |
| occurrences (all)                    | 1                | 4                | 0                |
| Migraine                             |                  |                  |                  |
| subjects affected / exposed          | 1 / 26 (3.85%)   | 3 / 27 (11.11%)  | 3 / 27 (11.11%)  |
| occurrences (all)                    | 2                | 3                | 3                |
| Tremor                               |                  |                  |                  |
| subjects affected / exposed          | 0 / 26 (0.00%)   | 2 / 27 (7.41%)   | 0 / 27 (0.00%)   |
| occurrences (all)                    | 0                | 2                | 0                |
| Blood and lymphatic system disorders |                  |                  |                  |
| Lymphadenopathy                      |                  |                  |                  |
| subjects affected / exposed          | 4 / 26 (15.38%)  | 1 / 27 (3.70%)   | 3 / 27 (11.11%)  |
| occurrences (all)                    | 7                | 1                | 3                |
| Ear and labyrinth disorders          |                  |                  |                  |
| Ear pain                             |                  |                  |                  |
| subjects affected / exposed          | 2 / 26 (7.69%)   | 2 / 27 (7.41%)   | 1 / 27 (3.70%)   |
| occurrences (all)                    | 2                | 2                | 1                |
| Eye disorders                        |                  |                  |                  |
| Eye pain                             |                  |                  |                  |
| subjects affected / exposed          | 0 / 26 (0.00%)   | 1 / 27 (3.70%)   | 0 / 27 (0.00%)   |
| occurrences (all)                    | 0                | 1                | 0                |
| Myopia                               |                  |                  |                  |
| subjects affected / exposed          | 0 / 26 (0.00%)   | 0 / 27 (0.00%)   | 2 / 27 (7.41%)   |
| occurrences (all)                    | 0                | 0                | 2                |

|                                                                          |                       |                      |                       |
|--------------------------------------------------------------------------|-----------------------|----------------------|-----------------------|
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)       | 2 / 26 (7.69%)<br>2   | 0 / 27 (0.00%)<br>0  | 1 / 27 (3.70%)<br>1   |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)       | 2 / 26 (7.69%)<br>2   | 4 / 27 (14.81%)<br>4 | 0 / 27 (0.00%)<br>0   |
| Gastrointestinal disorders                                               |                       |                      |                       |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 9 / 26 (34.62%)<br>17 | 5 / 27 (18.52%)<br>6 | 6 / 27 (22.22%)<br>12 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 7 / 26 (26.92%)<br>11 | 5 / 27 (18.52%)<br>8 | 3 / 27 (11.11%)<br>7  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 1 / 26 (3.85%)<br>1   | 3 / 27 (11.11%)<br>4 | 2 / 27 (7.41%)<br>2   |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 4 / 26 (15.38%)<br>10 | 4 / 27 (14.81%)<br>5 | 4 / 27 (14.81%)<br>7  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 1 / 26 (3.85%)<br>1   | 4 / 27 (14.81%)<br>4 | 4 / 27 (14.81%)<br>6  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 26 (0.00%)<br>0   | 3 / 27 (11.11%)<br>3 | 0 / 27 (0.00%)<br>0   |
| Stomach discomfort<br>subjects affected / exposed<br>occurrences (all)   | 1 / 26 (3.85%)<br>1   | 2 / 27 (7.41%)<br>2  | 3 / 27 (11.11%)<br>4  |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 2 / 26 (7.69%)<br>2   | 2 / 27 (7.41%)<br>2  | 0 / 27 (0.00%)<br>0   |
| Toothache<br>subjects affected / exposed<br>occurrences (all)            | 2 / 26 (7.69%)<br>2   | 0 / 27 (0.00%)<br>0  | 0 / 27 (0.00%)<br>0   |
| Skin and subcutaneous tissue disorders                                   |                       |                      |                       |

|                                                                                                                   |                      |                       |                      |
|-------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|----------------------|
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)                                            | 1 / 26 (3.85%)<br>1  | 1 / 27 (3.70%)<br>2   | 1 / 27 (3.70%)<br>1  |
| Skin hypertrophy<br>subjects affected / exposed<br>occurrences (all)                                              | 0 / 26 (0.00%)<br>0  | 1 / 27 (3.70%)<br>2   | 0 / 27 (0.00%)<br>0  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)                                                     | 2 / 26 (7.69%)<br>2  | 1 / 27 (3.70%)<br>1   | 3 / 27 (11.11%)<br>6 |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                                                        | 1 / 26 (3.85%)<br>1  | 0 / 27 (0.00%)<br>0   | 1 / 27 (3.70%)<br>1  |
| Keratosis pilaris<br>subjects affected / exposed<br>occurrences (all)                                             | 0 / 26 (0.00%)<br>0  | 0 / 27 (0.00%)<br>0   | 1 / 27 (3.70%)<br>1  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 26 (0.00%)<br>0  | 0 / 27 (0.00%)<br>0   | 2 / 27 (7.41%)<br>2  |
| Hair texture abnormal<br>subjects affected / exposed<br>occurrences (all)                                         | 0 / 26 (0.00%)<br>0  | 1 / 27 (3.70%)<br>1   | 2 / 27 (7.41%)<br>2  |
| Renal and urinary disorders<br>Enuresis<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 26 (3.85%)<br>1  | 1 / 27 (3.70%)<br>1   | 2 / 27 (7.41%)<br>2  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 26 (0.00%)<br>0  | 0 / 27 (0.00%)<br>0   | 2 / 27 (7.41%)<br>2  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 7 / 26 (26.92%)<br>8 | 4 / 27 (14.81%)<br>7  | 5 / 27 (18.52%)<br>5 |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                             | 4 / 26 (15.38%)<br>7 | 8 / 27 (29.63%)<br>11 | 7 / 27 (25.93%)<br>8 |
| Back pain                                                                                                         |                      |                       |                      |

|                                   |                  |                  |                 |
|-----------------------------------|------------------|------------------|-----------------|
| subjects affected / exposed       | 3 / 26 (11.54%)  | 5 / 27 (18.52%)  | 1 / 27 (3.70%)  |
| occurrences (all)                 | 4                | 5                | 1               |
| Musculoskeletal stiffness         |                  |                  |                 |
| subjects affected / exposed       | 0 / 26 (0.00%)   | 0 / 27 (0.00%)   | 0 / 27 (0.00%)  |
| occurrences (all)                 | 0                | 0                | 0               |
| Neck pain                         |                  |                  |                 |
| subjects affected / exposed       | 2 / 26 (7.69%)   | 0 / 27 (0.00%)   | 1 / 27 (3.70%)  |
| occurrences (all)                 | 2                | 0                | 1               |
| Scoliosis                         |                  |                  |                 |
| subjects affected / exposed       | 0 / 26 (0.00%)   | 0 / 27 (0.00%)   | 2 / 27 (7.41%)  |
| occurrences (all)                 | 0                | 0                | 2               |
| Muscle spasms                     |                  |                  |                 |
| subjects affected / exposed       | 0 / 26 (0.00%)   | 3 / 27 (11.11%)  | 1 / 27 (3.70%)  |
| occurrences (all)                 | 0                | 4                | 2               |
| Myalgia                           |                  |                  |                 |
| subjects affected / exposed       | 1 / 26 (3.85%)   | 2 / 27 (7.41%)   | 1 / 27 (3.70%)  |
| occurrences (all)                 | 2                | 4                | 1               |
| Infections and infestations       |                  |                  |                 |
| Upper respiratory tract infection |                  |                  |                 |
| subjects affected / exposed       | 10 / 26 (38.46%) | 10 / 27 (37.04%) | 9 / 27 (33.33%) |
| occurrences (all)                 | 23               | 19               | 31              |
| Otitis media                      |                  |                  |                 |
| subjects affected / exposed       | 4 / 26 (15.38%)  | 5 / 27 (18.52%)  | 3 / 27 (11.11%) |
| occurrences (all)                 | 4                | 7                | 5               |
| Viral infection                   |                  |                  |                 |
| subjects affected / exposed       | 6 / 26 (23.08%)  | 3 / 27 (11.11%)  | 6 / 27 (22.22%) |
| occurrences (all)                 | 10               | 6                | 6               |
| Gastroenteritis                   |                  |                  |                 |
| subjects affected / exposed       | 1 / 26 (3.85%)   | 3 / 27 (11.11%)  | 5 / 27 (18.52%) |
| occurrences (all)                 | 2                | 3                | 9               |
| Pharyngitis streptococcal         |                  |                  |                 |
| subjects affected / exposed       | 5 / 26 (19.23%)  | 12 / 27 (44.44%) | 7 / 27 (25.93%) |
| occurrences (all)                 | 13               | 17               | 9               |
| Gastroenteritis viral             |                  |                  |                 |
| subjects affected / exposed       | 6 / 26 (23.08%)  | 3 / 27 (11.11%)  | 2 / 27 (7.41%)  |
| occurrences (all)                 | 7                | 9                | 4               |

|                                         |                 |                 |                 |
|-----------------------------------------|-----------------|-----------------|-----------------|
| Influenza                               |                 |                 |                 |
| subjects affected / exposed             | 2 / 26 (7.69%)  | 3 / 27 (11.11%) | 5 / 27 (18.52%) |
| occurrences (all)                       | 2               | 4               | 6               |
| Ear infection                           |                 |                 |                 |
| subjects affected / exposed             | 3 / 26 (11.54%) | 2 / 27 (7.41%)  | 4 / 27 (14.81%) |
| occurrences (all)                       | 5               | 4               | 6               |
| Otitis externa                          |                 |                 |                 |
| subjects affected / exposed             | 1 / 26 (3.85%)  | 1 / 27 (3.70%)  | 0 / 27 (0.00%)  |
| occurrences (all)                       | 1               | 1               | 0               |
| Molluscum contagiosum                   |                 |                 |                 |
| subjects affected / exposed             | 2 / 26 (7.69%)  | 0 / 27 (0.00%)  | 0 / 27 (0.00%)  |
| occurrences (all)                       | 2               | 0               | 0               |
| Bronchitis                              |                 |                 |                 |
| subjects affected / exposed             | 1 / 26 (3.85%)  | 1 / 27 (3.70%)  | 2 / 27 (7.41%)  |
| occurrences (all)                       | 1               | 3               | 4               |
| Nasopharyngitis                         |                 |                 |                 |
| subjects affected / exposed             | 3 / 26 (11.54%) | 4 / 27 (14.81%) | 4 / 27 (14.81%) |
| occurrences (all)                       | 4               | 5               | 15              |
| Pharyngitis                             |                 |                 |                 |
| subjects affected / exposed             | 0 / 26 (0.00%)  | 2 / 27 (7.41%)  | 0 / 27 (0.00%)  |
| occurrences (all)                       | 0               | 3               | 0               |
| Sinusitis                               |                 |                 |                 |
| subjects affected / exposed             | 5 / 26 (19.23%) | 7 / 27 (25.93%) | 3 / 27 (11.11%) |
| occurrences (all)                       | 25              | 14              | 5               |
| Urinary tract infection                 |                 |                 |                 |
| subjects affected / exposed             | 0 / 26 (0.00%)  | 0 / 27 (0.00%)  | 1 / 27 (3.70%)  |
| occurrences (all)                       | 0               | 0               | 3               |
| Varicella                               |                 |                 |                 |
| subjects affected / exposed             | 0 / 26 (0.00%)  | 0 / 27 (0.00%)  | 0 / 27 (0.00%)  |
| occurrences (all)                       | 0               | 0               | 0               |
| Tonsillitis                             |                 |                 |                 |
| subjects affected / exposed             | 1 / 26 (3.85%)  | 1 / 27 (3.70%)  | 3 / 27 (11.11%) |
| occurrences (all)                       | 1               | 1               | 3               |
| Viral upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed             | 1 / 26 (3.85%)  | 3 / 27 (11.11%) | 0 / 27 (0.00%)  |
| occurrences (all)                       | 1               | 3               | 0               |



|                                    |                |                |                |
|------------------------------------|----------------|----------------|----------------|
| Metabolism and nutrition disorders |                |                |                |
| Hypoglycaemia                      |                |                |                |
| subjects affected / exposed        | 2 / 26 (7.69%) | 0 / 27 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all)                  | 3              | 0              | 0              |

|                                                                     |                                      |  |  |
|---------------------------------------------------------------------|--------------------------------------|--|--|
| <b>Non-serious adverse events</b>                                   | 45 µg/kg rhGH +<br>150 µg/kg rhIGF-1 |  |  |
| Total subjects affected by non-serious adverse events               |                                      |  |  |
| subjects affected / exposed                                         | 26 / 26 (100.00%)                    |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                      |  |  |
| Skin papilloma                                                      |                                      |  |  |
| subjects affected / exposed                                         | 4 / 26 (15.38%)                      |  |  |
| occurrences (all)                                                   | 5                                    |  |  |
| General disorders and administration site conditions                |                                      |  |  |
| Pyrexia                                                             |                                      |  |  |
| subjects affected / exposed                                         | 13 / 26 (50.00%)                     |  |  |
| occurrences (all)                                                   | 19                                   |  |  |
| Injection site pain                                                 |                                      |  |  |
| subjects affected / exposed                                         | 4 / 26 (15.38%)                      |  |  |
| occurrences (all)                                                   | 6                                    |  |  |
| Malaise                                                             |                                      |  |  |
| subjects affected / exposed                                         | 4 / 26 (15.38%)                      |  |  |
| occurrences (all)                                                   | 4                                    |  |  |
| Injection site bruising                                             |                                      |  |  |
| subjects affected / exposed                                         | 3 / 26 (11.54%)                      |  |  |
| occurrences (all)                                                   | 5                                    |  |  |
| Injection site hypertrophy                                          |                                      |  |  |
| subjects affected / exposed                                         | 3 / 26 (11.54%)                      |  |  |
| occurrences (all)                                                   | 4                                    |  |  |
| Injection site induration                                           |                                      |  |  |
| subjects affected / exposed                                         | 3 / 26 (11.54%)                      |  |  |
| occurrences (all)                                                   | 4                                    |  |  |
| Influenza like illness                                              |                                      |  |  |
| subjects affected / exposed                                         | 2 / 26 (7.69%)                       |  |  |
| occurrences (all)                                                   | 2                                    |  |  |
| Injection site erythema                                             |                                      |  |  |

|                                                                                                                                  |                                   |  |  |
|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                      | <p>2 / 26 (7.69%)</p> <p>3</p>    |  |  |
| <p>Injection site urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                      | <p>2 / 26 (7.69%)</p> <p>5</p>    |  |  |
| <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                       | <p>1 / 26 (3.85%)</p> <p>1</p>    |  |  |
| <p>Feeling hot</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                   | <p>0 / 26 (0.00%)</p> <p>0</p>    |  |  |
| <p>Immune system disorders</p> <p>Hypersensitivity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>               | <p>2 / 26 (7.69%)</p> <p>2</p>    |  |  |
| <p>Seasonal allergy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                              | <p>0 / 26 (0.00%)</p> <p>0</p>    |  |  |
| <p>Reproductive system and breast disorders</p> <p>Gynaecomastia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 26 (3.85%)</p> <p>1</p>    |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>10 / 26 (38.46%)</p> <p>14</p> |  |  |
| <p>Pharyngolaryngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                        | <p>5 / 26 (19.23%)</p> <p>5</p>   |  |  |
| <p>Nasal congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                              | <p>3 / 26 (11.54%)</p> <p>3</p>   |  |  |
| <p>Asthma</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                        | <p>2 / 26 (7.69%)</p> <p>2</p>    |  |  |
| <p>Epistaxis</p>                                                                                                                 |                                   |  |  |

|                                          |                |  |  |
|------------------------------------------|----------------|--|--|
| subjects affected / exposed              | 1 / 26 (3.85%) |  |  |
| occurrences (all)                        | 4              |  |  |
| Rhinitis allergic                        |                |  |  |
| subjects affected / exposed              | 1 / 26 (3.85%) |  |  |
| occurrences (all)                        | 1              |  |  |
| Rhinorrhoea                              |                |  |  |
| subjects affected / exposed              | 1 / 26 (3.85%) |  |  |
| occurrences (all)                        | 1              |  |  |
| Tonsillar hypertrophy                    |                |  |  |
| subjects affected / exposed              | 1 / 26 (3.85%) |  |  |
| occurrences (all)                        | 1              |  |  |
| Adenoidal hypertrophy                    |                |  |  |
| subjects affected / exposed              | 0 / 26 (0.00%) |  |  |
| occurrences (all)                        | 0              |  |  |
| Psychiatric disorders                    |                |  |  |
| Anxiety                                  |                |  |  |
| subjects affected / exposed              | 2 / 26 (7.69%) |  |  |
| occurrences (all)                        | 2              |  |  |
| Attention deficit/hyperactivity disorder |                |  |  |
| subjects affected / exposed              | 0 / 26 (0.00%) |  |  |
| occurrences (all)                        | 0              |  |  |
| Attention                                |                |  |  |
| subjects affected / exposed              | 0 / 26 (0.00%) |  |  |
| occurrences (all)                        | 0              |  |  |
| Investigations                           |                |  |  |
| Insulin-like growth factor increased     |                |  |  |
| subjects affected / exposed              | 2 / 26 (7.69%) |  |  |
| occurrences (all)                        | 4              |  |  |
| Body temperature increased               |                |  |  |
| subjects affected / exposed              | 1 / 26 (3.85%) |  |  |
| occurrences (all)                        | 1              |  |  |
| Hepatic enzyme increased                 |                |  |  |
| subjects affected / exposed              | 0 / 26 (0.00%) |  |  |
| occurrences (all)                        | 0              |  |  |
| Thyroxine free decreased                 |                |  |  |

|                                                |                 |  |  |
|------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                    | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Weight decreased                               |                 |  |  |
| subjects affected / exposed                    | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Injury, poisoning and procedural complications |                 |  |  |
| Procedural pain                                |                 |  |  |
| subjects affected / exposed                    | 3 / 26 (11.54%) |  |  |
| occurrences (all)                              | 3               |  |  |
| Arthropod sting                                |                 |  |  |
| subjects affected / exposed                    | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                              | 2               |  |  |
| Contusion                                      |                 |  |  |
| subjects affected / exposed                    | 1 / 26 (3.85%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Skin laceration                                |                 |  |  |
| subjects affected / exposed                    | 1 / 26 (3.85%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Upper limb fracture                            |                 |  |  |
| subjects affected / exposed                    | 1 / 26 (3.85%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Concussion                                     |                 |  |  |
| subjects affected / exposed                    | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Joint sprain                                   |                 |  |  |
| subjects affected / exposed                    | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Limb injury                                    |                 |  |  |
| subjects affected / exposed                    | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Orthodontic appliance complication             |                 |  |  |
| subjects affected / exposed                    | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Cardiac disorders                              |                 |  |  |

|                                                                                                             |                        |  |  |
|-------------------------------------------------------------------------------------------------------------|------------------------|--|--|
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                             | 2 / 26 (7.69%)<br>2    |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                    | 18 / 26 (69.23%)<br>50 |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                               | 2 / 26 (7.69%)<br>3    |  |  |
| Migraine<br>subjects affected / exposed<br>occurrences (all)                                                | 1 / 26 (3.85%)<br>7    |  |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                                                  | 1 / 26 (3.85%)<br>1    |  |  |
| Blood and lymphatic system disorders<br>Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all) | 1 / 26 (3.85%)<br>1    |  |  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 26 (7.69%)<br>2    |  |  |
| Eye disorders<br>Eye pain<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 26 (7.69%)<br>2    |  |  |
| Myopia<br>subjects affected / exposed<br>occurrences (all)                                                  | 1 / 26 (3.85%)<br>1    |  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 26 (3.85%)<br>1    |  |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                                          | 0 / 26 (0.00%)<br>0    |  |  |

|                                        |                  |  |  |
|----------------------------------------|------------------|--|--|
| Gastrointestinal disorders             |                  |  |  |
| Vomiting                               |                  |  |  |
| subjects affected / exposed            | 12 / 26 (46.15%) |  |  |
| occurrences (all)                      | 19               |  |  |
| Abdominal pain upper                   |                  |  |  |
| subjects affected / exposed            | 7 / 26 (26.92%)  |  |  |
| occurrences (all)                      | 11               |  |  |
| Diarrhoea                              |                  |  |  |
| subjects affected / exposed            | 6 / 26 (23.08%)  |  |  |
| occurrences (all)                      | 6                |  |  |
| Nausea                                 |                  |  |  |
| subjects affected / exposed            | 6 / 26 (23.08%)  |  |  |
| occurrences (all)                      | 11               |  |  |
| Abdominal pain                         |                  |  |  |
| subjects affected / exposed            | 2 / 26 (7.69%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Dyspepsia                              |                  |  |  |
| subjects affected / exposed            | 2 / 26 (7.69%)   |  |  |
| occurrences (all)                      | 4                |  |  |
| Stomach discomfort                     |                  |  |  |
| subjects affected / exposed            | 2 / 26 (7.69%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Abdominal discomfort                   |                  |  |  |
| subjects affected / exposed            | 0 / 26 (0.00%)   |  |  |
| occurrences (all)                      | 0                |  |  |
| Toothache                              |                  |  |  |
| subjects affected / exposed            | 0 / 26 (0.00%)   |  |  |
| occurrences (all)                      | 0                |  |  |
| Skin and subcutaneous tissue disorders |                  |  |  |
| Dermatitis contact                     |                  |  |  |
| subjects affected / exposed            | 3 / 26 (11.54%)  |  |  |
| occurrences (all)                      | 6                |  |  |
| Skin hypertrophy                       |                  |  |  |
| subjects affected / exposed            | 3 / 26 (11.54%)  |  |  |
| occurrences (all)                      | 3                |  |  |
| Urticaria                              |                  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 3 / 26 (11.54%) |  |  |
| occurrences (all)                               | 3               |  |  |
| Eczema                                          |                 |  |  |
| subjects affected / exposed                     | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Keratosis pilaris                               |                 |  |  |
| subjects affected / exposed                     | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Alopecia                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 26 (3.85%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Hair texture abnormal                           |                 |  |  |
| subjects affected / exposed                     | 1 / 26 (3.85%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Enuresis                                        |                 |  |  |
| subjects affected / exposed                     | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Pollakiuria                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 6 / 26 (23.08%) |  |  |
| occurrences (all)                               | 12              |  |  |
| Pain in extremity                               |                 |  |  |
| subjects affected / exposed                     | 5 / 26 (19.23%) |  |  |
| occurrences (all)                               | 12              |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 4 / 26 (15.38%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Musculoskeletal stiffness                       |                 |  |  |
| subjects affected / exposed                     | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Neck pain                                       |                 |  |  |

|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| subjects affected / exposed       | 2 / 26 (7.69%)   |  |  |
| occurrences (all)                 | 2                |  |  |
| Scoliosis                         |                  |  |  |
| subjects affected / exposed       | 2 / 26 (7.69%)   |  |  |
| occurrences (all)                 | 2                |  |  |
| Muscle spasms                     |                  |  |  |
| subjects affected / exposed       | 1 / 26 (3.85%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Myalgia                           |                  |  |  |
| subjects affected / exposed       | 1 / 26 (3.85%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Infections and infestations       |                  |  |  |
| Upper respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 13 / 26 (50.00%) |  |  |
| occurrences (all)                 | 37               |  |  |
| Otitis media                      |                  |  |  |
| subjects affected / exposed       | 9 / 26 (34.62%)  |  |  |
| occurrences (all)                 | 19               |  |  |
| Viral infection                   |                  |  |  |
| subjects affected / exposed       | 8 / 26 (30.77%)  |  |  |
| occurrences (all)                 | 21               |  |  |
| Gastroenteritis                   |                  |  |  |
| subjects affected / exposed       | 6 / 26 (23.08%)  |  |  |
| occurrences (all)                 | 10               |  |  |
| Pharyngitis streptococcal         |                  |  |  |
| subjects affected / exposed       | 6 / 26 (23.08%)  |  |  |
| occurrences (all)                 | 14               |  |  |
| Gastroenteritis viral             |                  |  |  |
| subjects affected / exposed       | 4 / 26 (15.38%)  |  |  |
| occurrences (all)                 | 4                |  |  |
| Influenza                         |                  |  |  |
| subjects affected / exposed       | 4 / 26 (15.38%)  |  |  |
| occurrences (all)                 | 4                |  |  |
| Ear infection                     |                  |  |  |
| subjects affected / exposed       | 3 / 26 (11.54%)  |  |  |
| occurrences (all)                 | 4                |  |  |



|                                         |                 |  |  |
|-----------------------------------------|-----------------|--|--|
| Otitis externa                          |                 |  |  |
| subjects affected / exposed             | 3 / 26 (11.54%) |  |  |
| occurrences (all)                       | 3               |  |  |
| Molluscum contagiosum                   |                 |  |  |
| subjects affected / exposed             | 3 / 26 (11.54%) |  |  |
| occurrences (all)                       | 3               |  |  |
| Bronchitis                              |                 |  |  |
| subjects affected / exposed             | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Nasopharyngitis                         |                 |  |  |
| subjects affected / exposed             | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                       | 3               |  |  |
| Pharyngitis                             |                 |  |  |
| subjects affected / exposed             | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Sinusitis                               |                 |  |  |
| subjects affected / exposed             | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Urinary tract infection                 |                 |  |  |
| subjects affected / exposed             | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Varicella                               |                 |  |  |
| subjects affected / exposed             | 2 / 26 (7.69%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Tonsillitis                             |                 |  |  |
| subjects affected / exposed             | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                       | 0               |  |  |
| Viral upper respiratory tract infection |                 |  |  |
| subjects affected / exposed             | 0 / 26 (0.00%)  |  |  |
| occurrences (all)                       | 0               |  |  |
| Metabolism and nutrition disorders      |                 |  |  |
| Hypoglycaemia                           |                 |  |  |
| subjects affected / exposed             | 7 / 26 (26.92%) |  |  |
| occurrences (all)                       | 8               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25 July 2008   | <ul style="list-style-type: none"><li>• The adiponectin test was deleted after failure to validate that assay;</li><li>• The number of sites was increased to 30;</li><li>• Language regarding the use of gonadotropin agonists (e.g., Lupron®) was clarified;</li><li>• Safety lab follow up for subjects with sustained IGF-1 SDS +4 was added;</li><li>• The possibility to use single injections of combination rhGH and rhIGF-1 during the first year was deleted;</li><li>• Addition of serum chemistry panel at Visit 4;</li><li>• Addition of gamma glutamyl transferase and creatine phosphokinase to the safety laboratory assessments, and additional growth factors as needed;</li><li>• Additional language added to risk management and reduction section regarding intracranial hypertension symptoms.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 11 August 2010 | <p>Amendment came into effect after all subjects had completed 1 year of treatment and following the availability of the first year height data contained in the interim report.</p> <ul style="list-style-type: none"><li>• The study duration for individual subjects was extended from 3 to 6 years to provide safety and efficacy data on longer-term use of combination rhGH and rhIGF-1. Updates to the protocol were made to reflect the extension to a six-year study;</li><li>• Minor changes were made to the wording of some of the study's secondary objectives.</li><li>• The primary efficacy endpoint of the study was clarified to only comprise the first year of the study and secondary efficacy endpoints for the subsequent years of the study were added;</li><li>• A new table of study assessments was added to reflect the extension to a six-year study. Insulin testing was removed from all future visits and collection of month and year of first menarche was added;</li><li>• The growth factor panel to be evaluated was modified to also include IGF-2 and insulin-like growth factor binding proteins other than IGFBP-1;</li><li>• The composition of the Data Monitoring Committee was changed;</li><li>• Text regarding resumption of study treatment after generalised allergic reaction, intracranial hypertension, hypoglycemia and subject monitoring was added to the Risk Management and reduction section;</li><li>• Protocol sections describing study assessments for each visit were modified in that pubertal status was added and specification of growth factors was replaced by "growth factor panel";</li><li>• Two additional protocol sections describing the study assessments to be performed at Visits 15 to 23 were added;</li><li>• Description of statistical method for assessment of total treatment effect for subjects with data beyond Year 1 and text regarding handling of missing data were added.</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated once the last subject had completed 3 years of treatment (compared to the 6 years planned) for strategic reasons.

Notes: