



## Clinical trial results:

### Efficacy and Safety of Somatropin in Combination With Leuporelin Compared to Somatropin Alone in Pubertal Children With Idiopathic Short Stature (Phoenix)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2005-001750-25 |
| Trial protocol           | NL             |
| Global end of trial date | 07 July 2015   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 26 August 2016 |
| First version publication date | 26 August 2016 |

#### Trial information

##### Trial identification

|                       |      |
|-----------------------|------|
| Sponsor protocol code | 9861 |
|-----------------------|------|

##### Additional study identifiers

|                                    |                                               |
|------------------------------------|-----------------------------------------------|
| ISRCTN number                      | -                                             |
| ClinicalTrials.gov id (NCT number) | NCT00266656                                   |
| WHO universal trial number (UTN)   | -                                             |
| Other trial identifiers            | Trial Number : 9861, Trial Alias: B9R-FP-GDGI |

Notes:

##### Sponsors

|                              |                                                                              |
|------------------------------|------------------------------------------------------------------------------|
| Sponsor organisation name    | Eli Lilly and Company                                                        |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285               |
| Public contact               | Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-CTLilly,  |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-285-4559, |

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                       | 07 July 2015 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 07 July 2015 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The present randomized trial was initially intended to study the benefits of a combined treatment with growth hormone (GH) and a gonadotropin-releasing hormone (GnRH) agonist for pubertal children with idiopathic short stature. However, treatments were stopped in January 2012 at the request of the French drug agency. Therefore, a protocol amendment divided the study in two study periods.

Study Period 1 involved combined treatment with somatropin and leuporelin or treatment with somatropin alone. Participants from France who participated in this Period 1 of the study were asked to participate in a long term safety follow up defined as a Period 2 of the study. Participants from the Netherlands were offered participation in Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS, clinicaltrials.gov Identifier: NCT01088412) for long term safety follow up independent of this study.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 26 June 2006 |
| Long term follow-up planned                               | Yes          |
| Long term follow-up rationale                             | Safety       |
| Long term follow-up duration                              | 42 Months    |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 11 |
| Country: Number of subjects enrolled | France: 77      |
| Worldwide total number of subjects   | 88              |
| EEA total number of subjects         | 88              |

Notes:

### Subjects enrolled per age group

|                                        |   |
|----------------------------------------|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|                                          |    |
|------------------------------------------|----|
| wk                                       |    |
| Newborns (0-27 days)                     | 0  |
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 42 |
| Adolescents (12-17 years)                | 46 |
| Adults (18-64 years)                     | 0  |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

No Text Entered

### Pre-assignment

Screening details:

No Text Entered

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                                               |
|------------------|-----------------------------------------------|
| <b>Arm title</b> | Somatropin and Leuporelin: Experimental Arm 1 |
|------------------|-----------------------------------------------|

Arm description:

0.05 milligram (mg) per kilogram (kg) per day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuporelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

|                                        |                     |
|----------------------------------------|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Somatropin          |
| Investigational medicinal product code |                     |
| Other name                             | LY137998, Humatrope |
| Pharmaceutical forms                   | Injection           |
| Routes of administration               | Subcutaneous use    |

Dosage and administration details:

0.05 milligram (mg) per kilogram (kg) per day

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

Dosage and administration details:

11.25 mg every 3 months

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Somatropin: Experimental Arm 2 |
|------------------|--------------------------------|

Arm description:

0.05mg/kg/day subcutaneous somatropin only.

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                     |
|----------------------------------------|---------------------|
| Investigational medicinal product name | Somatropin          |
| Investigational medicinal product code |                     |
| Other name                             | LY137998, Humatrope |
| Pharmaceutical forms                   | Injection           |
| Routes of administration               | Subcutaneous use    |

Dosage and administration details:

0.05 milligram (mg) per kilogram (kg) per day

| <b>Number of subjects in period 1</b>    | <b>Somatropin and Leuporelin: Experimental Arm 1</b> | <b>Somatropin: Experimental Arm 2</b> |
|------------------------------------------|------------------------------------------------------|---------------------------------------|
| Started                                  | 45                                                   | 43                                    |
| Received At Least One Dose of Study Drug | 45                                                   | 43                                    |
| Reached Final Height                     | 1 <sup>[1]</sup>                                     | 1 <sup>[2]</sup>                      |
| Did Not Reach Final Height               | 44                                                   | 42                                    |
| Completed                                | 20                                                   | 19                                    |
| Not completed                            | 25                                                   | 24                                    |
| See justification section                | 25                                                   | 24                                    |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to system limitations, the participants listed as completed/not completed are the participants who participated/did not participate in study period 2. The actual completed/not completed participants are 1/44 for arm 1.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to system limitations, the participants listed as completed/not completed are the participants who participated/did not participate in study period 2. The actual completed/not completed participants are 1/43 for arm 2.

## Period 2

|                              |                                    |
|------------------------------|------------------------------------|
| Period 2 title               | Study Period 2 Long Term Follow-Up |
| Is this the baseline period? | No                                 |
| Allocation method            | Not applicable                     |
| Blinding used                | Not blinded                        |

## Arms

|                              |                                               |
|------------------------------|-----------------------------------------------|
| Are arms mutually exclusive? | Yes                                           |
| <b>Arm title</b>             | Somatropin and Leuporelin: Experimental Arm 1 |

Arm description:

No treatment was administered during the follow up period. Participants received the following during the treatment period: 0.05mg/kg/day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuporelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

Participants from the Netherlands exited the study after Study Period 1. Participants from France were given the option to re-consent for Study Period 2.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                     |
|----------------------------------------|---------------------|
| Investigational medicinal product name | Somatropin          |
| Investigational medicinal product code |                     |
| Other name                             | LY137998, Humatrope |
| Pharmaceutical forms                   | Injection           |
| Routes of administration               | Subcutaneous use    |

Dosage and administration details:

0.05 milligram (mg) per kilogram (kg) per day

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

Dosage and administration details:

11.25 mg every 3 months

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Somatropin: Experimental Arm 2 |
|------------------|--------------------------------|

Arm description:

No treatment was administered during the follow up period. Participants received the following during the treatment period: 0.05mg/kg/day subcutaneous somatropin only.

Participants from the Netherlands exited the study after Study Period 1. Participants from France were given the option to re-consent for Study Period 2.

|                                        |                     |
|----------------------------------------|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Somatropin          |
| Investigational medicinal product code |                     |
| Other name                             | LY137998, Humatrope |
| Pharmaceutical forms                   | Injection           |
| Routes of administration               | Subcutaneous use    |

Dosage and administration details:

0.05 milligram (mg) per kilogram (kg) per day

| <b>Number of subjects in period 2</b> | Somatropin and<br>Leuprorelin:<br>Experimental Arm 1 | Somatropin:<br>Experimental Arm 2 |
|---------------------------------------|------------------------------------------------------|-----------------------------------|
| Started                               | 20                                                   | 19                                |
| Completed                             | 19                                                   | 17                                |
| Not completed                         | 1                                                    | 2                                 |
| Consent withdrawn by subject          | 1                                                    | 1                                 |
| Lost to follow-up                     | -                                                    | 1                                 |

## Baseline characteristics

### Reporting groups

|                       |                                               |
|-----------------------|-----------------------------------------------|
| Reporting group title | Somatropin and Leuporelin: Experimental Arm 1 |
|-----------------------|-----------------------------------------------|

Reporting group description:

0.05 milligram (mg) per kilogram (kg) per day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuporelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Somatropin: Experimental Arm 2 |
|-----------------------|--------------------------------|

Reporting group description:

0.05mg/kg/day subcutaneous somatropin only.

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

| Reporting group values                    | Somatropin and Leuporelin: Experimental Arm 1 | Somatropin: Experimental Arm 2 | Total |
|-------------------------------------------|-----------------------------------------------|--------------------------------|-------|
| Number of subjects                        | 45                                            | 43                             | 88    |
| Age categorical                           |                                               |                                |       |
| Units: Subjects                           |                                               |                                |       |
| Children (2-11 years)                     | 20                                            | 22                             | 42    |
| Adolescents (12-17 years)                 | 25                                            | 21                             | 46    |
| Age Continuous                            |                                               |                                |       |
| Units: years                              |                                               |                                |       |
| arithmetic mean                           | 12.1                                          | 12.1                           |       |
| standard deviation                        | ± 1.41                                        | ± 1.33                         | -     |
| Gender, Male/Female                       |                                               |                                |       |
| Units: participants                       |                                               |                                |       |
| Female                                    | 26                                            | 20                             | 46    |
| Male                                      | 19                                            | 23                             | 42    |
| Race (NIH/OMB)                            |                                               |                                |       |
| Units: Subjects                           |                                               |                                |       |
| American Indian or Alaska Native          | 0                                             | 0                              | 0     |
| Asian                                     | 4                                             | 2                              | 6     |
| Native Hawaiian or Other Pacific Islander | 0                                             | 0                              | 0     |
| Black or African American                 | 1                                             | 0                              | 1     |
| White                                     | 38                                            | 40                             | 78    |
| More than one race                        | 0                                             | 0                              | 0     |
| Unknown or Not Reported                   | 2                                             | 1                              | 3     |
| Region of Enrollment                      |                                               |                                |       |
| Units: Subjects                           |                                               |                                |       |
| Netherlands                               | 6                                             | 5                              | 11    |
| France                                    | 39                                            | 38                             | 77    |

|                                                                                                 |                 |                 |   |
|-------------------------------------------------------------------------------------------------|-----------------|-----------------|---|
| Standing Height SDS<br>Units: Standard Deviation Score<br>arithmetic mean<br>standard deviation | -2.5<br>± 0.45  | -2.5<br>± 0.46  | - |
| Standing Height<br>Units: centimeters<br>arithmetic mean<br>standard deviation                  | 131.6<br>± 6.72 | 131.6<br>± 5.78 | - |



## End points

### End points reporting groups

|                       |                                                |
|-----------------------|------------------------------------------------|
| Reporting group title | Somatropin and Leuprorelin: Experimental Arm 1 |
|-----------------------|------------------------------------------------|

Reporting group description:

0.05 milligram (mg) per kilogram (kg) per day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuprorelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Somatropin: Experimental Arm 2 |
|-----------------------|--------------------------------|

Reporting group description:

0.05mg/kg/day subcutaneous somatropin only.

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

|                       |                                                |
|-----------------------|------------------------------------------------|
| Reporting group title | Somatropin and Leuprorelin: Experimental Arm 1 |
|-----------------------|------------------------------------------------|

Reporting group description:

No treatment was administered during the follow up period. Participants received the following during the treatment period: 0.05mg/kg/day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuprorelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

Participants from the Netherlands exited the study after Study Period 1. Participants from France were given the option to re-consent for Study Period 2.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Somatropin: Experimental Arm 2 |
|-----------------------|--------------------------------|

Reporting group description:

No treatment was administered during the follow up period. Participants received the following during the treatment period: 0.05mg/kg/day subcutaneous somatropin only.

Participants from the Netherlands exited the study after Study Period 1. Participants from France were given the option to re-consent for Study Period 2.

|                            |                                                     |
|----------------------------|-----------------------------------------------------|
| Subject analysis set title | Arm: Somatropin and Leuprorelin: Experimental Arm 1 |
|----------------------------|-----------------------------------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All participants that started the study in addition to participants from previous control group who were ineligible to participate in the study were given somatropin and are included for AE assessment.

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Arm: Somatropin: Experimental Arm 2 |
|----------------------------|-------------------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All participants that started the study in addition to participants from previous control group who were ineligible to participate in the study were given somatropin and are included for AE assessment.

### Primary: Number of Participants With One Or More Drug-related Adverse Events

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Number of Participants With One Or More Drug-related Adverse Events <sup>[1]</sup> |
|-----------------|------------------------------------------------------------------------------------|

End point description:

A drug-related AE was an AE that occurred postdose or was present predose and became more severe postdose and was considered to be related to study treatment. A summary of other nonserious AEs, and all SAE's, regardless of causality, is located in the Reported Adverse Events section.

Population description: All participants who received at least one dose of study drug in Period 1 and all participants who entered Period 2 (safety population).

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

End point timeframe:

Baseline through End of Study (up to 9 years)

Notes:

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

Justification: No statistical analyses was planned after the discontinuation of treatments. Only descriptive statistics performed as participants were only followed up for safety.

| End point values            | Arm:<br>Somatropin<br>and<br>Leuporelin:<br>Experimental<br>Arm 1 | Arm:<br>Somatropin:<br>Experimental<br>Arm 2 |  |  |
|-----------------------------|-------------------------------------------------------------------|----------------------------------------------|--|--|
| Subject group type          | Subject analysis set                                              | Subject analysis set                         |  |  |
| Number of subjects analysed | 46                                                                | 45                                           |  |  |
| Units: participants         |                                                                   |                                              |  |  |
| number (not applicable)     |                                                                   |                                              |  |  |
| Study Period 1 (n=46, 45)   | 42                                                                | 38                                           |  |  |
| Study Period 2 (n=20, 19)   | 11                                                                | 9                                            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Adult Height Standard Deviation Score (SDS)

|                 |                                                            |
|-----------------|------------------------------------------------------------|
| End point title | Adult Height Standard Deviation Score (SDS) <sup>[2]</sup> |
|-----------------|------------------------------------------------------------|

End point description:

The height of the participants were measured barefoot using a standard wall-mounted Harpenden stadiometer. SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received at least one dose of study drug with at least one follow up visit.

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

End point timeframe:

Baseline through End of Study (up to 9 years)

Notes:

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

Justification: The analysis for the primary efficacy objective on adult height SDS was not performed due to the early termination of study treatment. However, the height of patients was still monitored up to adult height in both treatment groups.

| End point values                     | Somatropin<br>and<br>Leuporelin:<br>Experimental<br>Arm 1 | Somatropin:<br>Experimental<br>Arm 2 |  |  |
|--------------------------------------|-----------------------------------------------------------|--------------------------------------|--|--|
| Subject group type                   | Reporting group                                           | Reporting group                      |  |  |
| Number of subjects analysed          | 19                                                        | 16                                   |  |  |
| Units: standard deviation score      |                                                           |                                      |  |  |
| arithmetic mean (standard deviation) | -1.8 (± 0.53)                                             | -1.9 (± 0.77)                        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Height Velocity

|                 |                 |
|-----------------|-----------------|
| End point title | Height Velocity |
|-----------------|-----------------|

End point description:

Height velocity is the difference between 2 height measurements, divided by years elapsed between measurements.

Population description: All participants who received at least one dose of study drug with at least one follow up visit. The safety follow up participants did not reach final height at end of Period 1 unless final height is noted for participants that reached final height at the end of Period 1.

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

End point timeframe:

Baseline through End of Study (up to 9 years)

| End point values                                   | Somatropin and Leuporelin: Experimental Arm 1 | Somatropin: Experimental Arm 2 |  |  |
|----------------------------------------------------|-----------------------------------------------|--------------------------------|--|--|
| Subject group type                                 | Reporting group                               | Reporting group                |  |  |
| Number of subjects analysed                        | 45                                            | 43                             |  |  |
| Units: centimeter per year                         |                                               |                                |  |  |
| arithmetic mean (standard deviation)               |                                               |                                |  |  |
| Randomization (n=45, 43)                           | 7.8 (± 6.92)                                  | 7.4 (± 6.03)                   |  |  |
| Month 3 (n=45, 43)                                 | 9.9 (± 3.94)                                  | 10.6 (± 3.53)                  |  |  |
| Month 6 (n=45, 42)                                 | 8.1 (± 2.31)                                  | 9.7 (± 2.8)                    |  |  |
| Month 12 (n=44, 42)                                | 7 (± 1.64)                                    | 8.8 (± 2.33)                   |  |  |
| Month 18 (n=42, 42)                                | 6.6 (± 1.68)                                  | 8.4 (± 2.64)                   |  |  |
| Month 24 (n=37, 41)                                | 4.9 (± 1.33)                                  | 7.8 (± 3.36)                   |  |  |
| Month 30 (n=25, 25)                                | 6.2 (± 2.09)                                  | 5.8 (± 2.93)                   |  |  |
| Month 36 (n=18, 19)                                | 6.6 (± 3.25)                                  | 3.5 (± 2.71)                   |  |  |
| Month 42 (n=13, 14)                                | 5.7 (± 1.94)                                  | 3.7 (± 2.17)                   |  |  |
| Month 48 (n=7, 8)                                  | 5.4 (± 2.27)                                  | 2.9 (± 2.73)                   |  |  |
| Month 54 (n=1, 1)                                  | 6.3 (± 0)                                     | 7.1 (± 0)                      |  |  |
| Safety follow up 6 months (n=16, 9)                | 4.6 (± 2.08)                                  | 4.5 (± 2.45)                   |  |  |
| Safety follow up 12 months(n=15, 8)                | 2.9 (± 2.37)                                  | 2.3 (± 1.43)                   |  |  |
| Safety follow up 18 months (n=12, 4)               | 3.3 (± 1.69)                                  | 1.2 (± 1.2)                    |  |  |
| Safety follow up 24 months (n=9, 1)                | 2 (± 1.32)                                    | 2.5 (± 0)                      |  |  |
| Safety follow up 36 months (n=5, 0)                | 1.3 (± 0.53)                                  | 0 (± 0)                        |  |  |
| Safety follow up 42 months (n=2, 0)                | 2.1 (± 2.45)                                  | 0 (± 0)                        |  |  |
| Safety follow up 12 months (final height)(n=18,14) | 0.5 (± 0.86)                                  | 0.8 (± 1.59)                   |  |  |

|                                                    |                   |                   |  |  |
|----------------------------------------------------|-------------------|-------------------|--|--|
| Safety follow up 24 months (final height) (n=7,10) | 0.3 ( $\pm$ 0.77) | 0.3 ( $\pm$ 0.97) |  |  |
| Safety follow up 36 months (final height) (n=3,7)  | 0.9 ( $\pm$ 0.78) | 0.3 ( $\pm$ 0.6)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Height SDS

|                 |            |
|-----------------|------------|
| End point title | Height SDS |
|-----------------|------------|

End point description:

SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received at least one dose of study drug with at least one follow up visit. The safety follow up participants did not reach final height at end of Period 1 unless final height is noted for participants that reached final height at the end of Period 1.

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

End point timeframe:

Baseline through End of Study (up to 9 years)

| End point values                     | Somatropin and Leuporelin: Experimental Arm 1 | Somatropin: Experimental Arm 2 |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group                |  |  |
| Number of subjects analysed          | 45                                            | 43                             |  |  |
| Units: standard deviation score      |                                               |                                |  |  |
| arithmetic mean (standard deviation) |                                               |                                |  |  |
| Randomization (n=45, 43)             | -2.5 ( $\pm$ 0.45)                            | -2.5 ( $\pm$ 0.46)             |  |  |
| Month 3 (n=45, 43)                   | -2.4 ( $\pm$ 0.42)                            | -2.4 ( $\pm$ 0.47)             |  |  |
| Month 6 (n=45, 42)                   | -2.3 ( $\pm$ 0.48)                            | -2.2 ( $\pm$ 0.52)             |  |  |
| Month 12 (n=44, 42)                  | -2.2 ( $\pm$ 0.5)                             | -2 ( $\pm$ 0.57)               |  |  |
| Month 18 (n=42, 42)                  | -2.2 ( $\pm$ 0.53)                            | -1.9 ( $\pm$ 0.63)             |  |  |
| Month 24 (n=37, 41)                  | -2.3 ( $\pm$ 0.58)                            | -1.8 ( $\pm$ 0.67)             |  |  |
| Month 30 (n=25, 25)                  | -2.2 ( $\pm$ 0.63)                            | -2 ( $\pm$ 0.58)               |  |  |
| Month 36 (n=18, 19)                  | -2 ( $\pm$ 0.65)                              | -2 ( $\pm$ 0.68)               |  |  |
| Month 42 (n=13, 14)                  | -1.8 ( $\pm$ 0.68)                            | -1.9 ( $\pm$ 0.66)             |  |  |
| Month 48 (n=7, 8)                    | -1.6 ( $\pm$ 0.52)                            | -1.9 ( $\pm$ 0.65)             |  |  |
| Month 54 (n=1, 1)                    | -1 ( $\pm$ 0)                                 | -1.7 ( $\pm$ 0)                |  |  |
| Safety follow up 6 months (n=16, 9)  | -2.1 ( $\pm$ 0.65)                            | -1.7 ( $\pm$ 0.77)             |  |  |
| Safety follow up 12 months (n=15, 8) | -1.9 ( $\pm$ 0.55)                            | -1.7 ( $\pm$ 0.77)             |  |  |
| Safety follow up 18 months (n=12, 4) | -1.9 ( $\pm$ 0.63)                            | -1.9 ( $\pm$ 0.78)             |  |  |
| Safety follow up 24 months (n=9, 1)  | -1.9 ( $\pm$ 0.46)                            | -1.2 ( $\pm$ 0)                |  |  |
| Safety follow up 36 months (n=5, 0)  | -1.9 ( $\pm$ 0.67)                            | 0 ( $\pm$ 0)                   |  |  |
| Safety follow up 42 months (n=2, 0)  | -2.4 ( $\pm$ 0.18)                            | 0 ( $\pm$ 0)                   |  |  |

|                                                    |                    |                    |  |  |
|----------------------------------------------------|--------------------|--------------------|--|--|
| Safety follow up 12 months (final height)(n=18,14) | -1.9 ( $\pm$ 0.46) | -1.8 ( $\pm$ 0.71) |  |  |
| Safety follow up 24 months (final height) (n=7,10) | -1.6 ( $\pm$ 0.56) | -2 ( $\pm$ 0.79)   |  |  |
| Safety follow up 36 months (final height) (n=3,7)  | -1.2 ( $\pm$ 0.9)  | -2.2 ( $\pm$ 0.94) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Difference Between Adult Height SDS And Target Height SDS

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Difference Between Adult Height SDS And Target Height SDS |
|-----------------|-----------------------------------------------------------|

End point description:

This is the difference between the gender, age and country matched standard deviation score of adult height and standard deviation score of target height [calculated as (mother's height (SDS) + father's height (SDS))/2] for particular participant.

The height of the participants were measured barefoot using a standard wall-mounted Harpenden stadiometer. SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received who reached final height.

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

End point timeframe:

Baseline through End of Study (up to 9 years)

| End point values                     | Somatropin and Leuporelin: Experimental Arm 1 | Somatropin: Experimental Arm 2 |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group                |  |  |
| Number of subjects analysed          | 16                                            | 15                             |  |  |
| Units: standard deviation score      |                                               |                                |  |  |
| arithmetic mean (standard deviation) | -0.6 ( $\pm$ 0.89)                            | -1.2 ( $\pm$ 0.8)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Difference Between Adult Height SDS And Baseline Predicted Height SDS

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Difference Between Adult Height SDS And Baseline Predicted Height SDS |
|-----------------|-----------------------------------------------------------------------|

End point description:

This is the difference between the gender, age and country matched standard deviation score of adult height and standard deviation score of baseline predicted height [calculated using the Bayley-Pinneau

method based on height and bone age] for particular participant.

The height of the participants were measured barefoot using a standard wall-mounted Harpenden stadiometer. SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received who reached final height.

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

End point timeframe:

Baseline through End up Study (up to 9 years)

| End point values                     | Somatropin and Leuporelin: Experimental Arm 1 | Somatropin: Experimental Arm 2 |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group                |  |  |
| Number of subjects analysed          | 18                                            | 16                             |  |  |
| Units: standard deviation score      |                                               |                                |  |  |
| arithmetic mean (standard deviation) | 1.1 (± 0.96)                                  | 1.2 (± 0.7)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Difference Between Adult Height SDS And Baseline Height SDS

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Difference Between Adult Height SDS And Baseline Height SDS |
|-----------------|-------------------------------------------------------------|

End point description:

This is the difference between the gender, age and country matched standard deviation score of adult height and standard deviation score of baseline height for particular participant.

The height of the participants were measured barefoot using a standard wall-mounted Harpenden stadiometer. SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received who reached final height.

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

End point timeframe:

Baseline through End up Study (up to 9 years)

| End point values                     | Somatropin and Leuporelin: Experimental Arm 1 | Somatropin: Experimental Arm 2 |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group                |  |  |
| Number of subjects analysed          | 19                                            | 16                             |  |  |
| Units: standard deviation score      |                                               |                                |  |  |
| arithmetic mean (standard deviation) | 0.6 (± 0.59)                                  | 0.6 (± 0.67)                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Of Children With Normal Adult Height SDS

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | Percentage Of Children With Normal Adult Height SDS |
|-----------------|-----------------------------------------------------|

End point description:

Percentage of children with normal adult height SDS (greater than -2 SDS and less than +2 SDS).

Population description: All participants who received at least one dose of study drug with at least one follow up visit.

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

End point timeframe:

Baseline through End of Study (up to 9 years)

| End point values                  | Somatropin and Leuporelin: Experimental Arm 1 | Somatropin: Experimental Arm 2 |  |  |
|-----------------------------------|-----------------------------------------------|--------------------------------|--|--|
| Subject group type                | Reporting group                               | Reporting group                |  |  |
| Number of subjects analysed       | 45                                            | 43                             |  |  |
| Units: percentage of participants |                                               |                                |  |  |
| number (not applicable)           | 26.7                                          | 25.6                           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Age

|                 |          |
|-----------------|----------|
| End point title | Bone Age |
|-----------------|----------|

End point description:

Bone age measured using the X-Ray of left hand and wrist.

Population description: All participants who received at least one dose of study drug with at least one follow up visit. The safety follow up participants did not reach final height at end of Period 1 unless final height is noted for participants that reached final height at the end of Period 1.

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

---

End point timeframe:

Baseline through End of Study (up to 9 years)

---

| <b>End point values</b>                               | Somatropin<br>and<br>Leuporelin:<br>Experimental<br>Arm 1 | Somatropin:<br>Experimental<br>Arm 2 |  |  |
|-------------------------------------------------------|-----------------------------------------------------------|--------------------------------------|--|--|
| Subject group type                                    | Reporting group                                           | Reporting group                      |  |  |
| Number of subjects analysed                           | 45                                                        | 43                                   |  |  |
| Units: years                                          |                                                           |                                      |  |  |
| arithmetic mean (standard deviation)                  |                                                           |                                      |  |  |
| Randomization (n=45, 43)                              | 10.8 (± 1.58)                                             | 11 (± 1.45)                          |  |  |
| Month 12 (n=40, 41)                                   | 11.7 (± 1.59)                                             | 12.1 (± 1.12)                        |  |  |
| Month 24 (n=34, 37)                                   | 12.4 (± 1.32)                                             | 13.4 (± 1.09)                        |  |  |
| Month 36 (n=18, 18)                                   | 13.3 (± 1.49)                                             | 14.5 (± 1.64)                        |  |  |
| Month 48 (n=7, 8)                                     | 14.8 (± 1.33)                                             | 15.4 (± 1.27)                        |  |  |
| Safety follow up 6 months (n=16, 7)                   | 14.1 (± 1.11)                                             | 14.9 (± 0.81)                        |  |  |
| Safety follow up 18 months (n=12, 3)                  | 15.2 (± 1.25)                                             | 17 (± 1)                             |  |  |
| Safety follow up 36 months (n=5, 0)                   | 15.7 (± 1.04)                                             | 0 (± 0)                              |  |  |
| Safety follow up 12 months (final<br>height)(n=18,14) | 19.6 (± 14.53)                                            | 16.3 (± 1.27)                        |  |  |

### Statistical analyses

---

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

All participants that started the study in addition to 3 participants from previous control group who were ineligible to participate in the study were given somatropin and are included in somatropin arm for AE assessment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Somatropin: Experimental Arm 2 |
|-----------------------|--------------------------------|

Reporting group description: -

|                       |                                                |
|-----------------------|------------------------------------------------|
| Reporting group title | Somatropin and Leuprorelin: Experimental Arm 1 |
|-----------------------|------------------------------------------------|

Reporting group description: -

| Serious adverse events                                              | Somatropin:<br>Experimental Arm 2 | Somatropin and<br>Leuprorelin:<br>Experimental Arm 1 |  |
|---------------------------------------------------------------------|-----------------------------------|------------------------------------------------------|--|
| Total subjects affected by serious adverse events                   |                                   |                                                      |  |
| subjects affected / exposed                                         | 7 / 45 (15.56%)                   | 12 / 46 (26.09%)                                     |  |
| number of deaths (all causes)                                       | 0                                 | 0                                                    |  |
| number of deaths resulting from adverse events                      | 0                                 | 0                                                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |                                                      |  |
| histiocytosis                                                       |                                   |                                                      |  |
| alternative dictionary used:<br>MedDRA 18.0                         |                                   |                                                      |  |
| subjects affected / exposed                                         | 0 / 45 (0.00%)                    | 1 / 46 (2.17%)                                       |  |
| occurrences causally related to treatment / all                     | 0 / 0                             | 0 / 1                                                |  |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0                                                |  |
| Injury, poisoning and procedural complications                      |                                   |                                                      |  |
| fall                                                                |                                   |                                                      |  |
| alternative dictionary used:<br>MedDRA 18.0                         |                                   |                                                      |  |
| subjects affected / exposed                                         | 0 / 45 (0.00%)                    | 1 / 46 (2.17%)                                       |  |
| occurrences causally related to treatment / all                     | 0 / 0                             | 0 / 1                                                |  |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0                                                |  |
| fracture                                                            |                                   |                                                      |  |
| alternative dictionary used:<br>MedDRA 18.0                         |                                   |                                                      |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| joint dislocation                               |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| radius fracture                                 |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| road traffic accident                           |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| upper limb fracture                             |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| wrist fracture                                  |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Congenital, familial and genetic disorders      |                |                |  |
| congenital genital malformation                 |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                          | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| thyroglossal cyst                                    |                |                |  |
| alternative dictionary used: MedDRA 18.0             |                |                |  |
| subjects affected / exposed                          | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                             |                |                |  |
| migraine                                             |                |                |  |
| alternative dictionary used: MedDRA 18.0             |                |                |  |
| subjects affected / exposed                          | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| complication of device removal                       |                |                |  |
| alternative dictionary used: MedDRA 18.0             |                |                |  |
| subjects affected / exposed                          | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                                |                |                |  |
| agitation                                            |                |                |  |
| alternative dictionary used: MedDRA 18.0             |                |                |  |
| subjects affected / exposed                          | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| intentional self-injury                              |                |                |  |
| alternative dictionary used: MedDRA 18.0             |                |                |  |
| subjects affected / exposed                          | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| mental disorder                                      |                |                |  |
| alternative dictionary used: MedDRA 18.0             |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| suicidal ideation                               |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| nephrolithiasis                                 |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| renal colic                                     |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| appendiceal abscess                             |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| appendicitis                                    |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 2 / 45 (4.44%) | 2 / 46 (4.35%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| gastroenteritis                                 |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| peritonitis                                     |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| viral infection                                 |                |                |  |
| alternative dictionary used: MedDRA 18.0        |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Somatropin:<br>Experimental Arm 2 | Somatropin and<br>Leuporelin:<br>Experimental Arm 1 |  |
|-------------------------------------------------------|-----------------------------------|-----------------------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                   |                                                     |  |
| subjects affected / exposed                           | 36 / 45 (80.00%)                  | 41 / 46 (89.13%)                                    |  |
| Injury, poisoning and procedural complications        |                                   |                                                     |  |
| ligament sprain                                       |                                   |                                                     |  |
| alternative dictionary used: MedDRA 18.0              |                                   |                                                     |  |
| subjects affected / exposed                           | 1 / 45 (2.22%)                    | 3 / 46 (6.52%)                                      |  |
| occurrences (all)                                     | 1                                 | 3                                                   |  |
| Nervous system disorders                              |                                   |                                                     |  |
| headache                                              |                                   |                                                     |  |
| alternative dictionary used: MedDRA 18.0              |                                   |                                                     |  |
| subjects affected / exposed                           | 16 / 45 (35.56%)                  | 21 / 46 (45.65%)                                    |  |
| occurrences (all)                                     | 37                                | 51                                                  |  |
| General disorders and administration site conditions  |                                   |                                                     |  |
| injection site pain                                   |                                   |                                                     |  |
| alternative dictionary used: MedDRA 18.0              |                                   |                                                     |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                         |                                                                                                        |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--|
| subjects affected / exposed<br>occurrences (all)<br><br>pyrexia<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                  | 0 / 45 (0.00%)<br>0<br><br>5 / 45 (11.11%)<br>6                                                         | 8 / 46 (17.39%)<br>22<br><br>4 / 46 (8.70%)<br>4                                                       |  |
| Ear and labyrinth disorders<br>ear pain<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                          | 3 / 45 (6.67%)<br>4                                                                                     | 1 / 46 (2.17%)<br>5                                                                                    |  |
| Immune system disorders<br>hypersensitivity<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0 / 45 (0.00%)<br>0                                                                                     | 3 / 46 (6.52%)<br>3                                                                                    |  |
| Gastrointestinal disorders<br>abdominal pain<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)<br><br>abdominal pain upper<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)<br><br>diarrhoea<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)<br><br>nausea<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)<br><br>toothache<br>alternative dictionary used:<br>MedDRA 18.0 | 7 / 45 (15.56%)<br>18<br><br>4 / 45 (8.89%)<br>10<br><br>3 / 45 (6.67%)<br>3<br><br>2 / 45 (4.44%)<br>3 | 4 / 46 (8.70%)<br>4<br><br>3 / 46 (6.52%)<br>11<br><br>3 / 46 (6.52%)<br>14<br><br>3 / 46 (6.52%)<br>7 |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| <p>subjects affected / exposed</p> <p>0 / 45 (0.00%)</p> <p>3 / 46 (6.52%)</p> <p>occurrences (all)</p> <p>0</p> <p>7</p> <p>vomiting</p> <p>alternative dictionary used:<br/>MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>3 / 45 (6.67%)</p> <p>3 / 46 (6.52%)</p> <p>occurrences (all)</p> <p>5</p> <p>5</p>                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>cough</p> <p>alternative dictionary used:<br/>MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>6 / 45 (13.33%)</p> <p>3 / 46 (6.52%)</p> <p>occurrences (all)</p> <p>15</p> <p>4</p> <p>epistaxis</p> <p>alternative dictionary used:<br/>MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>2 / 45 (4.44%)</p> <p>3 / 46 (6.52%)</p> <p>occurrences (all)</p> <p>2</p> <p>4</p> <p>oropharyngeal pain</p> <p>alternative dictionary used:<br/>MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>4 / 45 (8.89%)</p> <p>5 / 46 (10.87%)</p> <p>occurrences (all)</p> <p>6</p> <p>6</p> |  |  |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>acne</p> <p>alternative dictionary used:<br/>MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>5 / 45 (11.11%)</p> <p>2 / 46 (4.35%)</p> <p>occurrences (all)</p> <p>7</p> <p>2</p>                                                                                                                                                                                                                                                                                                                                                                                                                    |  |  |  |
| <p>Endocrine disorders</p> <p>hypothyroidism</p> <p>alternative dictionary used:<br/>MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>3 / 45 (6.67%)</p> <p>1 / 46 (2.17%)</p> <p>occurrences (all)</p> <p>3</p> <p>1</p>                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>arthralgia</p> <p>alternative dictionary used:<br/>MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>4 / 45 (8.89%)</p> <p>7 / 46 (15.22%)</p> <p>occurrences (all)</p> <p>6</p> <p>11</p> <p>pain in extremity</p>                                                                                                                                                                                                                                                                                                                                                                           |  |  |  |

|                                                                                                                                              |                       |                        |  |
|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------|--|
| alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                              | 1 / 45 (2.22%)<br>1   | 4 / 46 (8.70%)<br>4    |  |
| scoliosis<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 45 (2.22%)<br>1   | 4 / 46 (8.70%)<br>4    |  |
| Infections and infestations<br>bronchitis<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all) | 2 / 45 (4.44%)<br>2   | 3 / 46 (6.52%)<br>4    |  |
| cystitis<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 45 (0.00%)<br>0   | 3 / 46 (6.52%)<br>3    |  |
| ear infection<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                             | 5 / 45 (11.11%)<br>8  | 4 / 46 (8.70%)<br>4    |  |
| gastroenteritis<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                           | 6 / 45 (13.33%)<br>9  | 11 / 46 (23.91%)<br>15 |  |
| influenza<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                 | 9 / 45 (20.00%)<br>16 | 15 / 46 (32.61%)<br>17 |  |
| nasopharyngitis<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                           | 8 / 45 (17.78%)<br>10 | 19 / 46 (41.30%)<br>36 |  |
| rhinitis<br>alternative dictionary used:<br>MedDRA 18.0                                                                                      |                       |                        |  |



|                                                                                                                                                               |                       |                      |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                              | 3 / 45 (6.67%)<br>11  | 5 / 46 (10.87%)<br>5 |  |
| tonsillitis<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                                | 5 / 45 (11.11%)<br>12 | 6 / 46 (13.04%)<br>9 |  |
| tracheitis<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all)                                                 | 3 / 45 (6.67%)<br>3   | 2 / 46 (4.35%)<br>2  |  |
| Metabolism and nutrition disorders<br>vitamin d deficiency<br>alternative dictionary used:<br>MedDRA 18.0<br>subjects affected / exposed<br>occurrences (all) | 0 / 45 (0.00%)<br>0   | 3 / 46 (6.52%)<br>3  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 January 2008 | Study Period 1 treatment with Humatrope was suspended for all active participants. Participants from the Netherlands exited the study after Study Period 1 and participants from France were given the option to re-consent for Study Period 2. |

Notes:

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### 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.

No statistical analyses was performed after the early treatment termination. All data represented is descriptive statistics only and no confirmatory conclusions can be drawn from this study.

Notes: