



## Clinical trial results:

### Long-Term Study of PNU-180307 For Short Children Born Small for Gestational Age (SGA) Without Epiphyseal Closure (Extension of The Study 307-MET-0021-002)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-004552-21 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 20 August 2015 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 12 August 2016 |
| First version publication date | 12 August 2016 |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | GENASG-0021-007 |
|-----------------------|-----------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Pfizer Inc.   |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017  |
| Public contact               | ClinicalTrials.gov_Inquiries@pfizer.com, Pfizer Inc., 1 8007181021, ClinicalTrials.govCallCenter@pfizer.com |
| Scientific contact           | ClinicalTrials.gov_Inquiries@pfizer.com, Pfizer Inc., 1 8007181021, ClinicalTrials.govCallCenter@pfizer.com |

Notes:

#### Paediatric regulatory details

|  |     |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No  |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

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**Results analysis stage**

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|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 20 August 2015 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 20 August 2015 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 20 August 2015 |
| Was the trial ended prematurely?                     | No             |

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective is to evaluate safety of long-term administration of PNU-180307 (Genotropin) until a final height is reached in short children born small for gestational age (SGA) without epiphyseal closure

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 14 October 2002 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 61 |
| Worldwide total number of subjects   | 61        |
| EEA total number of subjects         | 0         |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                     | 61 |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Before enrolled this study, participants with short stature due to SGA had completed the 1-year(12-month) treatment in previous study.

### Period 1

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

### Arms

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

Arm description:

Participants who were treated with somatropin 0.033 mg/kg/day in previous study for 12 months received a dose of 0.067 mg/kg/day

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

Dosage and administration details:

0.067 mg/kg/day

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Dose-Remaining Group |
|------------------|----------------------|

Arm description:

Participants who were treated with somatropin 0.067 mg/kg/day in previous study for 12 months were maintained on the same dose

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

Dosage and administration details:

0.067 mg/kg/day

| <b>Number of subjects in period 1</b> | <b>Dose-Increasing Group</b> | <b>Dose-Remaining Group</b> |
|---------------------------------------|------------------------------|-----------------------------|
| Started                               | 29                           | 32                          |
| Completed                             | 15                           | 15                          |
| Not completed                         | 14                           | 17                          |
| Physician decision                    | 2                            | 4                           |
| Consent withdrawn by subject          | 11                           | 10                          |
| Adverse event, non-fatal              | -                            | 1                           |
| Family Matters                        | -                            | 1                           |
| Protocol deviation                    | 1                            | 1                           |

## Baseline characteristics

### Reporting groups

|  |                       |
|--|-----------------------|
| Reporting group title  | Dose-Increasing Group |
| Reporting group description:<br>Participants who were treated with somatropin 0.033 mg/kg/day in previous study for 12 months received a dose of 0.067 mg/kg/day |                       |
| Reporting group title  | Dose-Remaining Group  |
| Reporting group description:<br>Participants who were treated with somatropin 0.067 mg/kg/day in previous study for 12 months were maintained on the same dose   |                       |

| Reporting group values                             | Dose-Increasing Group | Dose-Remaining Group | Total |
|--|-----------------------|----------------------|-------|
| Number of subjects                                 | 29                    | 32                   | 61    |
| Age categorical<br>Units: Subjects                 |                       |                      |       |
| In utero   | 0                     | 0                    | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                     | 0                    | 0     |
| Newborns (0-27 days)                               | 0                     | 0                    | 0     |
| Infants and toddlers (28 days-23 months)           | 0                     | 0                    | 0     |
| Children (2-11 years)                              | 29                    | 32                   | 61    |
| Adolescents (12-17 years)                          | 0                     | 0                    | 0     |
| Adults (18-64 years)                               | 0                     | 0                    | 0     |
| From 65-84 years                                   | 0                     | 0                    | 0     |
| 85 years and over                                  | 0                     | 0                    | 0     |
| Age Continuous  <br>Units: years                   |                       |                      |       |
| arithmetic mean                                    | 5.2                   | 5.4                  |       |
| standard deviation                                 | ± 1.64                | ± 1.27               | -     |
| Gender, Male/Female<br>Units: Participants         |                       |                      |       |
| Female   | 14                    | 14                   | 28    |
| Male   | 15                    | 18                   | 33    |

## End points

### End points reporting groups

|  |                       |
|--|-----------------------|
| Reporting group title  | Dose-Increasing Group |
| Reporting group description:<br>Participants who were treated with somatropin 0.033 mg/kg/day in previous study for 12 months received a dose of 0.067 mg/kg/day |                       |
| Reporting group title  | Dose-Remaining Group  |
| Reporting group description:<br>Participants who were treated with somatropin 0.067 mg/kg/day in previous study for 12 months were maintained on the same dose   |                       |

### Primary: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

|  |  |
|--|--|
| End point title  | Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs) |
| End point description:   |  |
| End point type   | Primary  |
| End point timeframe:<br>Month 12 (at the end of previous study) to 156 |  |

| End point values            | Dose-Increasing Group | Dose-Remaining Group |  |  |
|-----------------------------|-----------------------|----------------------|--|--|
| Subject group type          | Reporting group       | Reporting group      |  |  |
| Number of subjects analysed | 29                    | 32                   |  |  |
| Units: participant          |                       |                      |  |  |
| AE                          | 27                    | 31                   |  |  |
| SAE                         | 10                    | 5                    |  |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | The number of participants with adverse event |
| Statistical analysis description:<br>The number of participants with adverse event by treatment group was tabulated by system organ class and by preferred term. |   |
| Comparison groups  | Dose-Increasing Group v Dose-Remaining Group  |
| Number of subjects included in analysis  | 61  |
| Analysis specification   | Pre-specified                                 |
| Analysis type  | other   |
| Parameter estimate   | Number of participants with AE                |
| Point estimate   | 0   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | Other: 0 %                 |
| sides                | 2-sided                    |
| lower limit          | 0                          |
| upper limit          | 0                          |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0                          |

## Secondary: Height Velocity Standard Deviation Score (SDS) for Chronological Age

|  |  |
|--|--|
| End point title  | Height Velocity Standard Deviation Score (SDS) for Chronological Age |
| End point description:   |  |
| Height velocity is the yearly height gain. Height velocity SDS is calculated as following formula; Height velocity SDS = (height velocity - mean) / standard deviation, where mean and standard deviation were based on standard Japanese values of the participants age and gender. The scores were centred around zero. Negative score indicated a participant was smaller for their age/gender. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Month 12 (at the end of previous study) to 156   |  |

| End point values                                | Dose-Increasing Group | Dose-Remaining Group |  |  |
|---|-----------------------|----------------------|--|--|
| Subject group type                              | Reporting group       | Reporting group      |  |  |
| Number of subjects analysed                     | 29                    | 32                   |  |  |
| Units: SDS                                      |                       |                      |  |  |
| arithmetic mean (standard deviation)            |                       |                      |  |  |
| Month 12-24 (Increasing:n=28, Remaining:n=32)   | 2.782 (± 1.978)       | 2.595 (± 1.731)      |  |  |
| Month 24-36 (Increasing:n=26, Remaining:n=28)   | 1.812 (± 1.526)       | 1.696 (± 2.111)      |  |  |
| Month 36-48 (Increasing:n=24, Remaining:n=23)   | 1.48 (± 1.543)        | 0.824 (± 1.527)      |  |  |
| Month 48-60 (Increasing:n=21, Remaining:n=20)   | -0.041 (± 2.081)      | 0.48 (± 1.651)       |  |  |
| Month 60-72 (Increasing:n=20, Remaining:n=16)   | -0.293 (± 1.585)      | -0.046 (± 2.434)     |  |  |
| Month 72-84 (Increasing:n=15, Remaining:n=16)   | -0.488 (± 3.117)      | -1.511 (± 2.692)     |  |  |
| Month 84-96 (Increasing: n=11, Remaining: n=14) | 0.263 (± 1.802)       | -0.114 (± 1.964)     |  |  |
| Month 96-108 (Increasing:n=9, Remaining:n=8)    | 0.521 (± 2.058)       | -0.466 (± 2.055)     |  |  |
| Month 108-120 (Increasing:n=6, Remaining:n=6)   | -0.668 (± 2.126)      | -0.59 (± 2.693)      |  |  |
| Month 120-132 (Increasing:n=5, Remaining:n=4)   | -1.08 (± 1.953)       | 1.173 (± 3.042)      |  |  |
| Month 132-144 (Increasing:n=4, Remaining:n=2)   | 2.655 (± 4.329)       | 0.73 (± 2.022)       |  |  |
| Month 144-156 (Increasing:n=3, Remaining:n=0)   | 3.373 (± 1.995)       | 0 (± 0)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Height Velocity

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

End point description:

Height velocity is the yearly height gain

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

End point timeframe:

Month 12 (at the end of previous study) to 156

| End point values                               | Dose-Increasing Group | Dose-Remaining Group |  |  |
|--|-----------------------|----------------------|--|--|
| Subject group type                             | Reporting group       | Reporting group      |  |  |
| Number of subjects analysed                    | 29                    | 32                   |  |  |
| Units: cm/year                                 |                       |                      |  |  |
| arithmetic mean (standard deviation)           |                       |                      |  |  |
| Month 12-24(Increasing:n=28, Remaining:n=32)   | 7.83 (± 1.33)         | 7.7 (± 1.19)         |  |  |
| Month 24-36 (Increasing:n=26, Remaining:n=28)  | 6.88 (± 0.94)         | 6.75 (± 1.52)        |  |  |
| Month 36-48 (Increasing:n=24, Remaining:n=23)  | 6.68 (± 0.98)         | 6.08 (± 1.14)        |  |  |
| Month 48-60 (Increasing:n=21, Remaining:n=20)  | 6.06 (± 1.49)         | 6.3 (± 1.24)         |  |  |
| Month 60-72 (Increasing:n=20, Remaining: n=16) | 6.08 (± 1.45)         | 6.49 (± 1.37)        |  |  |
| Month 72-84 (Increasing:n=15, Remaining:n=16)  | 4.89 (± 2.18)         | 4.88 (± 1.86)        |  |  |
| Month 84-96 (Increasing:n=11, Remaining:n=14)  | 5.16 (± 1.2)          | 4.82 (± 2.12)        |  |  |
| Month 96-108 (Increasing:n=9, Remaining:n=8)   | 5.18 (± 2.16)         | 5.55 (± 2.42)        |  |  |
| Month 108-120 (Increasing:n=6, Remaining:n=6)  | 5.72 (± 2.24)         | 5.03 (± 1.86)        |  |  |
| Month 120-132 (Increasing:n=5, Remaining:n=4)  | 4.84 (± 1.3)          | 4.3 (± 1.84)         |  |  |
| Month 132-144 (Increasing:n=4, Remaining:n=2)  | 4.38 (± 1.1)          | 2.6 (± 0.14)         |  |  |
| Month144-156(Increasing:n=3, Remaining:n=0)    | 3.1 (± 1.92)          | 0 (± 0)              |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Height SDS for Chronological Age

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Height SDS for Chronological Age |
|-----------------|----------------------------------|

End point description:

Height SDS is calculated as following formula; Height SDS = (height - mean) / standard deviation, where mean and standard deviation were based on standard Japanese values on the participant age and gender. The scores were centred around zero. Negative score indicated a participant was smaller for their age/gender.

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

End point timeframe:

Month 12 (at the end of previous study) to 156

| End point values                           | Dose-Increasing Group | Dose-Remaining Group |  |  |
|--|-----------------------|----------------------|--|--|
| Subject group type                         | Reporting group       | Reporting group      |  |  |
| Number of subjects analysed                | 29                    | 32                   |  |  |
| Units: SDS                                 |                       |                      |  |  |
| arithmetic mean (standard deviation)       |                       |                      |  |  |
| Month 12 (Increasing:n=29, Remaining:n=32) | -2.53 (± 0.92)        | -2.17 (± 0.96)       |  |  |
| Month 24 (Increasing:n=28, Remaining:n=32) | -2.02 (± 0.97)        | -1.7 (± 1.03)        |  |  |
| Month 36 (Increasing:n=26, Remaining:n=28) | -1.8 (± 0.99)         | -1.53 (± 1.1)        |  |  |
| Month 48 (Increasing:n=24, Remaining:n=23) | -1.48 (± 1.05)        | -1.49 (± 1.15)       |  |  |
| Month 60 (Increasing:n=21, Remaining:n=20) | -1.53 (± 1.06)        | -1.44 (± 1.1)        |  |  |
| Month 72 (Increasing:n=20, Remaining:n=16) | -1.56 (± 1.11)        | -1.43 (± 1.06)       |  |  |
| Month 84 (Increasing:n=15, Remaining:n=16) | -1.73 (± 1.13)        | -1.58 (± 1.17)       |  |  |
| Month 96 (Increasing:n=11, Remaining:n=14) | -1.52 (± 0.89)        | -1.87 (± 1.36)       |  |  |
| Month 108 (Increasing:n=9, Remaining:n=8)  | -1.52 (± 1.01)        | -1.63 (± 1.48)       |  |  |
| Month 120 (Increasing:n=6, Remaining:n=6)  | -1.52 (± 1.2)         | -1.25 (± 0.59)       |  |  |
| Month 132 (Increasing:n=5, Remaining:n=4)  | -1.96 (± 1.11)        | -0.98 (± 0.51)       |  |  |
| Month 144 (Increasing:n=4, Remaining:n=2)  | -1.73 (± 0.87)        | -0.7 (± 0.42)        |  |  |
| Month 156 (Increasing:n=3, Remaining:n=0)  | -1.77 (± 0.76)        | 0 (± 0)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Height Velocity SDS for Bone Age

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Height Velocity SDS for Bone Age |
|-----------------|----------------------------------|

End point description:

To measure bone age, X-ray images of the left hand were centrally assessed by an independent specialist using the Tanner-Whitehouse 2 (RUS) method standardized for Japanese children. Height velocity is the yearly height gain. Height velocity SDS for bone age is calculated as following formula; Height velocity SDS = (height velocity - mean) / standard deviation, where mean and standard deviation were based on standard Japanese values corresponding to bone age and gender. The scores were centred around zero. Negative score indicated a participant was smaller for their age/gender.

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

End point timeframe:

Month 12 (at the end of previous study) to 156

| End point values                                | Dose-Increasing Group | Dose-Remaining Group |  |  |
|---|-----------------------|----------------------|--|--|
| Subject group type                              | Reporting group       | Reporting group      |  |  |
| Number of subjects analysed                     | 29                    | 32                   |  |  |
| Units: SDS                                      |                       |                      |  |  |
| arithmetic mean (standard deviation)            |                       |                      |  |  |
| Month 12-24 (Increasing: n=26, Remaining: n=31) | 2.586 (± 2.268)       | 2.461 (± 1.99)       |  |  |
| Month 24-36 (Increasing: n=24, Remaining: n=27) | 1.503 (± 1.83)        | 1.091 (± 1.852)      |  |  |
| Month 36-48 (Increasing: n=22, Remaining: n=22) | 1.196 (± 1.409)       | 0.51 (± 1.809)       |  |  |
| Month 48-60 (Increasing: n=20, Remaining: n=19) | -0.062 (± 1.775)      | 0.913 (± 2.146)      |  |  |
| Month 60-72 (Increasing: n=16, Remaining: n=14) | 0.281 (± 2.814)       | 0.949 (± 2.729)      |  |  |
| Month 72-84 (Increasing: n=13, Remaining: n=13) | -1.249 (± 2.558)      | 0.932 (± 2.545)      |  |  |
| Month 84-96 (Increasing: n=10, Remaining: n=13) | 0.804 (± 3.44)        | 0.286 (± 2.351)      |  |  |
| Month 96-108 (Increasing: n=8, Remaining: n=7)  | -0.634 (± 2.419)      | -0.223 (± 1.352)     |  |  |
| Month 108-120 (Increasing: n=5, Remaining: n=5) | 0.07 (± 4.12)         | 0.532 (± 1.809)      |  |  |
| Month 120-132 (Increasing: n=4, Remaining: n=4) | 1.553 (± 3.019)       | 2.718 (± 0.864)      |  |  |
| Month 132-144 (Increasing: n=3, Remaining: n=2) | 2.31 (± 1.711)        | 2.185 (± 0.304)      |  |  |
| Month 144-156 (Increasing: n=2, Remaining: n=0) | 2.71 (± 2.942)        | 0 (± 0)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Height SDS for Bone Age

|                 |                         |
|-----------------|-------------------------|
| End point title | Height SDS for Bone Age |
|-----------------|-------------------------|

**End point description:**

To measure bone age, X-ray images of the left hand were centrally assessed by an independent specialist using the Tanner-Whitehouse 2 (RUS) method standardized for Japanese children. Height SDS for bone age is calculated as following formula; Height SDS = (height - mean) / standard deviation, where mean and standard deviation were based on standard Japanese values corresponding to bone age and gender. The scores were centred around zero. Negative score indicated a participant was smaller for their age/gender.

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

**End point timeframe:**

Month 12 (at the end of previous study) to 156

| <b>End point values</b>                      | Dose-Increasing Group | Dose-Remaining Group |  |  |
|--|-----------------------|----------------------|--|--|
| Subject group type                           | Reporting group       | Reporting group      |  |  |
| Number of subjects analysed                  | 29                    | 32                   |  |  |
| Units: SDS                                   |                       |                      |  |  |
| arithmetic mean (standard deviation)         |                       |                      |  |  |
| Month 12 (Increasing: n=27, Remaining: n=31) | -1.19 (± 1.2)         | -0.68 (± 1.54)       |  |  |
| Month 24 (Increasing: n=26, Remaining: n=31) | -1.15 (± 1.15)        | -0.88 (± 1.79)       |  |  |
| Month 36 (Increasing: n=24, Remaining: n=27) | -1.2 (± 1.35)         | -1.17 (± 1.62)       |  |  |
| Month 48 (Increasing: n=22, Remaining: n=22) | -0.74 (± 1.32)        | -1.46 (± 1.01)       |  |  |
| Month 60 (Increasing: n=20, Remaining: n=19) | -1.16 (± 1.21)        | -1.8 (± 0.97)        |  |  |
| Month 72 (Increasing: n=16, Remaining: n=14) | -1.78 (± 1.02)        | -1.7 (± 0.77)        |  |  |
| Month 84 (Increasing: n=13, Remaining: n=13) | -1.85 (± 1.17)        | -2.15 (± 0.92)       |  |  |
| Month 96 (Increasing: n=10, Remaining: n=13) | -1.77 (± 1.12)        | -2.27 (± 1.06)       |  |  |
| Month 108 (Increasing: n=8, Remaining: n=7)  | -1.41 (± 0.97)        | -1.94 (± 1.37)       |  |  |
| Month 120 (Increasing: n=5, Remaining: n=5)  | -1.58 (± 1.5)         | -1.38 (± 0.98)       |  |  |
| Month 132 (Increasing: n=4, Remaining: n=4)  | -2.1 (± 1.21)         | -0.98 (± 0.74)       |  |  |
| Month 144 (Increasing: n=3, Remaining: n=2)  | -1.4 (± 0.17)         | -0.65 (± 0.64)       |  |  |
| Month 156 (Increasing: n=2, Remaining: n=0)  | -1.55 (± 0.92)        | 0 (± 0)              |  |  |

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Month 12 (at the end of previous study) to 156

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

### Dictionary used

|                 |                    |
|-----------------|--------------------|
| Dictionary name | WHO-ART, 2001(014) |
|-----------------|--------------------|

|                    |            |
|--------------------|------------|
| Dictionary version | 2001 (014) |
|--------------------|------------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Dose-Remainig Group |
|-----------------------|---------------------|

Reporting group description:

Participants in the 0.067 mg/kg/day group in previous study were maintained on the dose in this expention study

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Dose-Increasing Group |
|-----------------------|-----------------------|

Reporting group description:

Participants who were treated with somatropin 0.033 mg/kg/day in previous study for 12 months received a dose of 0.067 mg/kg/day

| Serious adverse events                               | Dose-Remainig Group | Dose-Increasing Group |  |
|--|---------------------|-----------------------|--|
| Total subjects affected by serious adverse events    |                     |                       |  |
| subjects affected / exposed                          | 5 / 32 (15.63%)     | 10 / 29 (34.48%)      |  |
| number of deaths (all causes)                        | 0                   | 0                     |  |
| number of deaths resulting from adverse events       | 0                   | 0                     |  |
| Congenital, familial and genetic disorders           |                     |                       |  |
| HYPOSPADIAS  |                     |                       |  |
| subjects affected / exposed                          | 0 / 32 (0.00%)      | 1 / 29 (3.45%)        |  |
| occurrences causally related to treatment / all      | 0 / 0               | 0 / 1                 |  |
| deaths causally related to treatment / all           | 0 / 0               | 0 / 0                 |  |
| CRYPTORCHISM   |                     |                       |  |
| subjects affected / exposed                          | 0 / 32 (0.00%)      | 1 / 29 (3.45%)        |  |
| 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 |                     |                       |  |
| INFLECTED INJURY                                     |                     |                       |  |
| subjects affected / exposed                          | 0 / 32 (0.00%)      | 1 / 29 (3.45%)        |  |
| occurrences causally related to treatment / all      | 0 / 0               | 0 / 1                 |  |
| deaths causally related to treatment / all           | 0 / 0               | 0 / 0                 |  |

|  |                                  |                                  |  |
|--|----------------------------------|----------------------------------|--|
| Ear and labyrinth disorders<br>DEAFNESS<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                        | 0 / 32 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 29 (3.45%)<br>0 / 1<br>0 / 0 |  |
| Eye disorders<br>RETINAL DETACHMENT<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                            | 1 / 32 (3.13%)<br>0 / 1<br>0 / 0 | 0 / 29 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Gastrointestinal disorders<br>GASTROENTERITIS<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                  | 0 / 32 (0.00%)<br>0 / 0<br>0 / 0 | 2 / 29 (6.90%)<br>0 / 2<br>0 / 0 |  |
| Reproductive system and breast disorders<br>HERNIA INGUINAL<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all    | 1 / 32 (3.13%)<br>0 / 1<br>0 / 0 | 1 / 29 (3.45%)<br>0 / 1<br>0 / 0 |  |
| OVARIAN DISORDER<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 0 / 32 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 29 (3.45%)<br>0 / 1<br>0 / 0 |  |
| Hepatobiliary disorders<br>HEPATIC FUNCTION ABNORMAL<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all           | 0 / 32 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 29 (3.45%)<br>0 / 1<br>0 / 0 |  |
| Respiratory, thoracic and mediastinal disorders<br>PHARYNGITIS<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 2 / 32 (6.25%)<br>0 / 2<br>0 / 0 | 1 / 29 (3.45%)<br>1 / 1<br>0 / 0 |  |
| PNEUMONIA  |                                  |                                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| UPPER RESP TRACT INFECTION                      |                |                |  |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| BRONCHITIS                                      |                |                |  |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ASTHMA  |                |                |  |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Endocrine disorders                             |                |                |  |
| ADENOID HYPERTROPHY                             |                |                |  |
| subjects affected / exposed                     | 2 / 32 (6.25%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| INFECTION VIRAL                                 |                |                |  |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 29 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| OTITIS MEDIA                                    |                |                |  |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 1 / 29 (3.45%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HEALING IMPAIRED                                |                |                |  |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 29 (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>                     | <b>Dose-Remaining Group</b> | <b>Dose-Increasing Group</b> |  |
|---|-----------------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events |                             |                              |  |
| subjects affected / exposed                           | 31 / 32 (96.88%)            | 27 / 29 (93.10%)             |  |
| General disorders and administration site conditions  |                             |                              |  |
| PURPURA   |                             |                              |  |
| subjects affected / exposed                           | 5 / 32 (15.63%)             | 6 / 29 (20.69%)              |  |
| occurrences (all)                                     | 8                           | 6                            |  |
| HAEMATOMA   |                             |                              |  |
| subjects affected / exposed                           | 0 / 32 (0.00%)              | 2 / 29 (6.90%)               |  |
| occurrences (all)                                     | 0                           | 2                            |  |
| ALLERGIC REACTION                                     |                             |                              |  |
| subjects affected / exposed                           | 3 / 32 (9.38%)              | 0 / 29 (0.00%)               |  |
| occurrences (all)                                     | 9                           | 0                            |  |
| FEVER   |                             |                              |  |
| subjects affected / exposed                           | 1 / 32 (3.13%)              | 11 / 29 (37.93%)             |  |
| occurrences (all)                                     | 3                           | 18                           |  |
| PAIN  |                             |                              |  |
| subjects affected / exposed                           | 2 / 32 (6.25%)              | 0 / 29 (0.00%)               |  |
| occurrences (all)                                     | 2                           | 0                            |  |
| INFLUENZA-LIKE SYMPTOMS                               |                             |                              |  |
| subjects affected / exposed                           | 15 / 32 (46.88%)            | 16 / 29 (55.17%)             |  |
| occurrences (all)                                     | 28                          | 24                           |  |
| VARICELLA   |                             |                              |  |
| subjects affected / exposed                           | 2 / 32 (6.25%)              | 3 / 29 (10.34%)              |  |
| occurrences (all)                                     | 2                           | 3                            |  |
| INFLECTED INJURY                                      |                             |                              |  |
| subjects affected / exposed                           | 4 / 32 (12.50%)             | 2 / 29 (6.90%)               |  |
| occurrences (all)                                     | 5                           | 2                            |  |
| MOLLUSCUM CONTAGIOSUM                                 |                             |                              |  |
| subjects affected / exposed                           | 2 / 32 (6.25%)              | 0 / 29 (0.00%)               |  |
| occurrences (all)                                     | 4                           | 0                            |  |
| SCOLIOSIS   |                             |                              |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)<br><br>LACERATION<br>subjects affected / exposed<br>occurrences (all)   | 2 / 32 (6.25%)<br>2<br><br>3 / 32 (9.38%)<br>3  | 1 / 29 (3.45%)<br>1<br><br>1 / 29 (3.45%)<br>1   |  |
| Reproductive system and breast disorders<br>OVARIAN DISORDER<br>subjects affected / exposed<br>occurrences (all)   | 0 / 32 (0.00%)<br>0   | 3 / 29 (10.34%)<br>4   |  |
| Respiratory, thoracic and mediastinal disorders<br>COUGHING<br>subjects affected / exposed<br>occurrences (all)<br><br>PHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>PNEUMONIA<br>subjects affected / exposed<br>occurrences (all)<br><br>RHINITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>SINUSITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>UPPER RESP TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all)<br><br>BRONCHITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>ASTHMA<br>subjects affected / exposed<br>occurrences (all) | 2 / 32 (6.25%)<br>2<br><br>9 / 32 (28.13%)<br>16<br><br>2 / 32 (6.25%)<br>3<br><br>12 / 32 (37.50%)<br>29<br><br>4 / 32 (12.50%)<br>6<br><br>28 / 32 (87.50%)<br>157<br><br>10 / 32 (31.25%)<br>25<br><br>6 / 32 (18.75%)<br>34 | 0 / 29 (0.00%)<br>0<br><br>7 / 29 (24.14%)<br>9<br><br>1 / 29 (3.45%)<br>1<br><br>8 / 29 (27.59%)<br>14<br><br>5 / 29 (17.24%)<br>6<br><br>25 / 29 (86.21%)<br>214<br><br>9 / 29 (31.03%)<br>31<br><br>6 / 29 (20.69%)<br>20 |  |
| Injury, poisoning and procedural complications   |   |  |  |



|   |                      |                      |  |
|---|----------------------|----------------------|--|
| INJECTION SITE BLEEDING<br>subjects affected / exposed<br>occurrences (all)   | 0 / 32 (0.00%)<br>0  | 2 / 29 (6.90%)<br>2  |  |
| STING<br>subjects affected / exposed<br>occurrences (all)   | 4 / 32 (12.50%)<br>4 | 1 / 29 (3.45%)<br>1  |  |
| Congenital, familial and genetic disorders<br>SKELETAL MALFORMATION<br>subjects affected / exposed<br>occurrences (all) | 2 / 32 (6.25%)<br>2  | 0 / 29 (0.00%)<br>0  |  |
| TOOTH MALFORMATION<br>subjects affected / exposed<br>occurrences (all)  | 1 / 32 (3.13%)<br>1  | 2 / 29 (6.90%)<br>2  |  |
| Cardiac disorders<br>HYPOTENSION POSTURAL<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 32 (3.13%)<br>1  | 2 / 29 (6.90%)<br>2  |  |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)                                | 3 / 32 (9.38%)<br>4  | 4 / 29 (13.79%)<br>5 |  |
| Blood and lymphatic system disorders<br>EOSINOPHILIA<br>subjects affected / exposed<br>occurrences (all)                | 3 / 32 (9.38%)<br>4  | 2 / 29 (6.90%)<br>7  |  |
| LEUKOCYTOSIS<br>subjects affected / exposed<br>occurrences (all)  | 4 / 32 (12.50%)<br>5 | 2 / 29 (6.90%)<br>3  |  |
| LYMPHADENOPATHY<br>subjects affected / exposed<br>occurrences (all)   | 3 / 32 (9.38%)<br>3  | 1 / 29 (3.45%)<br>1  |  |
| LYMPHOCYTES ATYPICA<br>subjects affected / exposed<br>occurrences (all)   | 0 / 32 (0.00%)<br>0  | 2 / 29 (6.90%)<br>2  |  |
| Eye disorders   |                      |                      |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| CONJUNCTIVITIS              |                  |                  |  |
| subjects affected / exposed | 12 / 32 (37.50%) | 8 / 29 (27.59%)  |  |
| occurrences (all)           | 16               | 17               |  |
| EYE ABNORMALITY             |                  |                  |  |
| subjects affected / exposed | 5 / 32 (15.63%)  | 4 / 29 (13.79%)  |  |
| occurrences (all)           | 8                | 5                |  |
| MYOPIA                      |                  |                  |  |
| subjects affected / exposed | 0 / 32 (0.00%)   | 2 / 29 (6.90%)   |  |
| occurrences (all)           | 0                | 2                |  |
| Gastrointestinal disorders  |                  |                  |  |
| CONSTIPATION                |                  |                  |  |
| subjects affected / exposed | 4 / 32 (12.50%)  | 3 / 29 (10.34%)  |  |
| occurrences (all)           | 6                | 5                |  |
| DIARRHOEA                   |                  |                  |  |
| subjects affected / exposed | 2 / 32 (6.25%)   | 5 / 29 (17.24%)  |  |
| occurrences (all)           | 2                | 5                |  |
| VOMITING                    |                  |                  |  |
| subjects affected / exposed | 3 / 32 (9.38%)   | 5 / 29 (17.24%)  |  |
| occurrences (all)           | 3                | 7                |  |
| ABDOMINAL PAIN              |                  |                  |  |
| subjects affected / exposed | 2 / 32 (6.25%)   | 0 / 29 (0.00%)   |  |
| occurrences (all)           | 2                | 0                |  |
| GASTROENTERITIS             |                  |                  |  |
| subjects affected / exposed | 10 / 32 (31.25%) | 17 / 29 (58.62%) |  |
| occurrences (all)           | 22               | 34               |  |
| NAUSEA                      |                  |                  |  |
| subjects affected / exposed | 2 / 32 (6.25%)   | 1 / 29 (3.45%)   |  |
| occurrences (all)           | 2                | 1                |  |
| STOMATITIS                  |                  |                  |  |
| subjects affected / exposed | 1 / 32 (3.13%)   | 2 / 29 (6.90%)   |  |
| occurrences (all)           | 3                | 6                |  |
| TOOTH CARIES                |                  |                  |  |
| subjects affected / exposed | 2 / 32 (6.25%)   | 4 / 29 (13.79%)  |  |
| occurrences (all)           | 2                | 6                |  |
| TOOTH DISORDER              |                  |                  |  |

|  |                       |                       |  |
|--|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 3 / 32 (9.38%)<br>3   | 1 / 29 (3.45%)<br>1   |  |
| ENTEROCOLITIS<br>subjects affected / exposed<br>occurrences (all)                                  | 2 / 32 (6.25%)<br>2   | 0 / 29 (0.00%)<br>0   |  |
| Hepatobiliary disorders<br>SGOT INCREASED<br>subjects affected / exposed<br>occurrences (all)      | 1 / 32 (3.13%)<br>1   | 3 / 29 (10.34%)<br>3  |  |
| SGPT INCREASED<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 32 (3.13%)<br>1   | 3 / 29 (10.34%)<br>3  |  |
| Skin and subcutaneous tissue disorders<br>ACNE<br>subjects affected / exposed<br>occurrences (all) | 3 / 32 (9.38%)<br>3   | 2 / 29 (6.90%)<br>2   |  |
| DERMATITIS<br>subjects affected / exposed<br>occurrences (all)                                     | 2 / 32 (6.25%)<br>3   | 3 / 29 (10.34%)<br>12 |  |
| ECZEMA<br>subjects affected / exposed<br>occurrences (all)   | 5 / 32 (15.63%)<br>10 | 6 / 29 (20.69%)<br>20 |  |
| PRURITUS<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 32 (6.25%)<br>2   | 0 / 29 (0.00%)<br>0   |  |
| RASH<br>subjects affected / exposed<br>occurrences (all)   | 1 / 32 (3.13%)<br>1   | 3 / 29 (10.34%)<br>4  |  |
| RASH ERYTHEMATOUS<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 32 (3.13%)<br>1   | 2 / 29 (6.90%)<br>2   |  |
| RASH PUSTULAR<br>subjects affected / exposed<br>occurrences (all)                                  | 2 / 32 (6.25%)<br>2   | 4 / 29 (13.79%)<br>4  |  |
| SKIN DISORDER  |                       |                       |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 32 (3.13%)<br>1  | 3 / 29 (10.34%)<br>3 |  |
| URTICARIA<br>subjects affected / exposed<br>occurrences (all)   | 2 / 32 (6.25%)<br>4  | 2 / 29 (6.90%)<br>2  |  |
| DERMATITIS CONTACT<br>subjects affected / exposed<br>occurrences (all)  | 2 / 32 (6.25%)<br>2  | 0 / 29 (0.00%)<br>0  |  |
| OTITIS EXTERNA<br>subjects affected / exposed<br>occurrences (all)  | 2 / 32 (6.25%)<br>2  | 3 / 29 (10.34%)<br>3 |  |
| BULLOUS ERUPTION<br>subjects affected / exposed<br>occurrences (all)  | 2 / 32 (6.25%)<br>2  | 2 / 29 (6.90%)<br>3  |  |
| VERRUCA<br>subjects affected / exposed<br>occurrences (all)   | 4 / 32 (12.50%)<br>5 | 1 / 29 (3.45%)<br>1  |  |
| Renal and urinary disorders<br>URINARY INCONTINENCE<br>subjects affected / exposed<br>occurrences (all)           | 0 / 32 (0.00%)<br>0  | 2 / 29 (6.90%)<br>2  |  |
| HAEMATURIA<br>subjects affected / exposed<br>occurrences (all)  | 3 / 32 (9.38%)<br>6  | 0 / 29 (0.00%)<br>0  |  |
| Endocrine disorders<br>SIALOADENITIS<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 32 (6.25%)<br>2  | 3 / 29 (10.34%)<br>3 |  |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all) | 5 / 32 (15.63%)<br>7 | 4 / 29 (13.79%)<br>4 |  |
| Infections and infestations<br>INFECTION BACTERIAL<br>subjects affected / exposed<br>occurrences (all)            | 6 / 32 (18.75%)<br>9 | 4 / 29 (13.79%)<br>8 |  |

|                                    |                  |                  |  |
|------------------------------------|------------------|------------------|--|
| INFECTION VIRAL                    |                  |                  |  |
| subjects affected / exposed        | 0 / 32 (0.00%)   | 2 / 29 (6.90%)   |  |
| occurrences (all)                  | 0                | 2                |  |
| OTITIS MEDIA                       |                  |                  |  |
| subjects affected / exposed        | 14 / 32 (43.75%) | 13 / 29 (44.83%) |  |
| occurrences (all)                  | 31               | 32               |  |
| HERPES ZOSTER                      |                  |                  |  |
| subjects affected / exposed        | 1 / 32 (3.13%)   | 2 / 29 (6.90%)   |  |
| occurrences (all)                  | 4                | 2                |  |
| ABSCESS                            |                  |                  |  |
| subjects affected / exposed        | 2 / 32 (6.25%)   | 0 / 29 (0.00%)   |  |
| occurrences (all)                  | 3                | 0                |  |
| Metabolism and nutrition disorders |                  |                  |  |
| GLUCOSE TOLERANCE ABNORMAL         |                  |                  |  |
| subjects affected / exposed        | 3 / 32 (9.38%)   | 1 / 29 (3.45%)   |  |
| occurrences (all)                  | 3                | 1                |  |

## **More information**

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

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported