



Clinical trial results:

Somatropin Therapy for Short Children Born of Premature Gestation: A Controlled, Prospective Randomized, Multicenter Study with an Untreated Control Group

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2004-004781-33 |
| Trial protocol | DE |
| Global end of trial date | 24 March 2010 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 15 April 2016 |
| First version publication date | 17 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A6281273 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00174460 |
| 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 | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 1800 7181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 1800 7181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 September 2010 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 March 2010 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine whether Growth Hormone (GH) therapy improves growth velocity and height Standard Deviation Score (SDS) after one year in very low birth weight (VLBW) preterm infants born appropriate-for-gestational age (AGA) with short stature.

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 | 29 August 2005 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 33 |
| Worldwide total number of subjects | 33 |
| EEA total number of subjects | 33 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 33 |
| 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:

The study started on 29-Aug-2005 and ended on 30-Sep-2010. There were 33 subjects enrolled in this study in Germany.

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Somatropin |

Arm description:

The children were randomized into a treated group receiving subcutaneous somatropin according to exact body weight specific calculation.

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

Dosage and administration details:

The children received 0.068 mg/kg/day (0.48mg/kg/week) subcutaneous somatropin according to exact body weight specific calculation. Dose adjustments were made at 6 month intervals. (mg=milligrams, kg=kilograms).

| | |
|------------------|-------------|
| Arm title | Control Arm |
|------------------|-------------|

Arm description:

The children were randomized into control group and after 1 year underwent Growth Hormone (GH) therapy, with subcutaneous somatropin according to exact body weight specific calculation.

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

Dosage and administration details:

Control group after 1 year underwent GH therapy with 0.068 mg/kg/day (0.48mg/kg/week) subcutaneous somatropin according to exact body weight specific calculation.

| Number of subjects in period 1 | Somatropin | Control Arm |
|---------------------------------------|------------|-------------|
| Started | 18 | 15 |
| Completed | 18 | 14 |
| Not completed | 0 | 1 |
| Consent withdrawn by subject | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Somatropin |
|-----------------------|------------|

Reporting group description:

The children were randomized into a treated group receiving subcutaneous somatropin according to exact body weight specific calculation.

| | |
|-----------------------|-------------|
| Reporting group title | Control Arm |
|-----------------------|-------------|

Reporting group description:

The children were randomized into control group and after 1 year underwent Growth Hormone (GH) therapy, with subcutaneous somatropin according to exact body weight specific calculation.

| Reporting group values | Somatropin | Control Arm | Total |
|---|------------|-------------|-------|
| Number of subjects | 18 | 15 | 33 |
| Age categorical | | | |
| 1 subject in each treatment group was below the age of 4 at screening. However, both of them were 4 years old when treatment began; they did not violate the corresponding inclusion criterion. | | | |
| Units: Subjects | | | |
| Less than (<) 4 years | 1 | 1 | 2 |
| Greater than or equal to ≥ 4 years and < 8 years | 14 | 11 | 25 |
| ≥ 8 years and < 12 years | 3 | 3 | 6 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 5.4 | 5.7 | |
| standard deviation | ± 1.6 | ± 1.9 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 7 | 16 |
| Male | 9 | 8 | 17 |

End points

End points reporting groups

| | |
|---|-------------|
| Reporting group title | Somatropin |
| Reporting group description: The children were randomized into a treated group receiving subcutaneous somatropin according to exact body weight specific calculation. | |
| Reporting group title | Control Arm |
| Reporting group description: The children were randomized into control group and after 1 year underwent Growth Hormone (GH) therapy, with subcutaneous somatropin according to exact body weight specific calculation. | |

Primary: Change in Height Standard Deviation Score (SDS) After 1 Year

| | |
|---|--|
| End point title | Change in Height Standard Deviation Score (SDS) After 1 Year |
| End point description: Change in Height SDS after 1 year where SDS = height minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). Full Analysis Set (FAS); all randomized subjects who had at least 1 post-baseline efficacy measurement; Control group received Somatropin from Month 12 onwards. | |
| End point type | Primary |
| End point timeframe: Baseline to 1 year (Month 12) | |

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: centimeters | | | | |
| least squares mean (standard error) | 1.099 (\pm 0.0714) | 0.108 (\pm 0.0783) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment difference for change in height SDS |
| Statistical analysis description: Results from analysis of covariance method (ANCOVA) adjusted for baseline height SDS and target height SDS; Last observation carried forward (LOCF). | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.991 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.773 |
| upper limit | 1.21 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1067 |

Primary: Change in Growth Velocity Standard Deviation Score (SDS) After 1 Year

| | |
|---|---|
| End point title | Change in Growth Velocity Standard Deviation Score (SDS) After 1 Year |
| End point description: Change in Growth Velocity (GV) SDS after 1 year where SDS= GV minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). FAS; Control group received Somatropin from Month 12 onwards. | |
| End point type | Primary |
| End point timeframe: Baseline to 1 year (Month 12) | |

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: centimeters per year | | | | |
| least squares mean (standard error) | 7.117 (\pm 0.4384) | 1.502 (\pm 0.4814) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment difference in growth velocity SDS |
| Statistical analysis description: Results from ANCOVA adjusted for baseline growth velocity SDS and target height SDS; LOCF. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 5.615 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.266 |
| upper limit | 6.963 |

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|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.6591 |

Secondary: Change From Baseline in Growth Velocity After 1 Year and After 2 Years

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|-----------------|--|
| End point title | Change From Baseline in Growth Velocity After 1 Year and After 2 Years |
|-----------------|--|

End point description:

Growth velocity measured as centimeters per year. FAS; Control group received Somatropin from Month 12 onwards.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: centimeter per year | | | | |
| least squares mean (standard error) | | | | |
| Month 12 | 5.11 (\pm 0.2623) | 0.695 (\pm 0.2881) | | |
| Month 24 | 3.049 (\pm 0.3546) | 3.934 (\pm 0.3893) | | |

Statistical analyses

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|----------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 12 |
|----------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline growth velocity, target height SDS, sex, and age; LOCF.

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|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.415 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.605 |
| upper limit | 5.225 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.395 |

| | |
|--|--------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
| Statistical analysis description: Results from ANCOVA adjusted for baseline growth velocity, target height SDS, sex, and age; LOCF. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.108 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.884 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.977 |
| upper limit | 0.208 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5327 |

Secondary: Change From Baseline in Growth Velocity SDS After 2 Years

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|---|---|
| End point title | Change From Baseline in Growth Velocity SDS After 2 Years |
| End point description: Change in Growth Velocity SDS after 2 years (24 months) where SDS = growth velocity minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). FAS; Control group received Somatropin from Month 12 onwards. | |
| End point type | Secondary |
| End point timeframe: Baseline, Month 24 | |

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: centimeter per year | | | | |
| least squares mean (standard error) | 4.751 (± 0.4716) | 5.825 (± 0.5177) | | |

Statistical analyses

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|---|---|
| Statistical analysis title | Change From Baseline in Growth Velocity SDS |
| Statistical analysis description: Results from ANCOVA adjusted for baseline growth velocity SDS and target height SDS; LOCF. | |

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|---|--------------------------------|
| Comparison groups | Control Arm v Somatropin |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.141 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.074 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.524 |
| upper limit | 0.376 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7089 |

Secondary: Change From Baseline in Height After 1 Year and After 2 Years

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|------------------------|---|
| End point title | Change From Baseline in Height After 1 Year and After 2 Years |
| End point description: | FAS; Control group received Somatropin from Month 12 onwards. |
| End point type | Secondary |
| End point timeframe: | Baseline, Month 12, Month 24 |

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: centimeters | | | | |
| least squares mean (standard error) | | | | |
| Month 12 | 10.467 (± 0.2439) | 5.927 (± 0.2677) | | |
| Month 24 | 18.908 (± 0.6507) | 14.844 (± 0.7149) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Treatment difference Month 12 |
| Statistical analysis description: | Results from ANCOVA adjusted for baseline height, target height SDS, sex, and age; LOCF. |
| Comparison groups | Somatropin v Control Arm |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.789 |
| upper limit | 5.291 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3661 |

| | |
|--|--------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline height, target height SDS, sex, and age; LOCF. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.064 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.049 |
| upper limit | 6.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.9822 |

Secondary: Change From Baseline in Height SDS After 2 Years

| | |
|---|--|
| End point title | Change From Baseline in Height SDS After 2 Years |
| End point description: | |
| Change in Height SDS after 2 years (24 months) where SDS = height minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). FAS; Control group received Somatropin from Month 12 onwards. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Month 24 | |

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: centimeters | | | | |
| least squares mean (standard error) | 1.71 (\pm 0.1075) | 0.991 (\pm 0.1179) | | |

Statistical analyses

| Statistical analysis title | Change From Baseline in Height SDS |
|---|------------------------------------|
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline height SDS and target height SDS; LOCF. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.719 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 1.047 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1606 |

Secondary: Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Triceps

| End point title | Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Triceps |
|---|---|
| End point description: | |
| Body composition measured as skinfold thickness at tricep in millimeters (mm); measured halfway down the left upper arm with arm hanging in relaxed position at subject's side. FAS; Control group received Somatropin from Month 12 onwards. Here n signifies the number of subjects evaluable at specific time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Month 12, Month 24 | |

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: millimeters | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n=15, 14) | -2.2 (± 0.341) | 0.5 (± 0.353) | | |
| Month 24 (n=16, 14) | -1.3 (± 0.511) | -0.83 (± 0.548) | | |

Statistical analyses

| Statistical analysis title | Treatment difference Month 12 |
|--|--------------------------------|
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, age, and sex; LOCF. For the treatment comparison, results were presented for 29 Subjects. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.73 |
| upper limit | -1.68 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.497 |

| Statistical analysis title | Treatment difference Month 24 |
|--|--------------------------------|
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, age, and sex; LOCF. For the treatment comparison, results were presented for 30 Subjects. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.537 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.48 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.04 |
| upper limit | 1.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.758 |

Secondary: Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Subscapular

| | |
|-----------------|---|
| End point title | Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Subscapular |
|-----------------|---|

End point description:

Body composition measured as subscapular skinfold thickness in mm; measured laterally just below the angle of the left scapula. FAS; Control group received Somatropin from Month 12 onwards. Here n signifies the number of subjects evaluable at specific time point.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: millimeters | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n= 15, 14) | 0.51 (± 0.783) | 0.45 (± 0.849) | | |
| Month 24 (n=16, 14) | 0.9 (± 0.688) | 0.79 (± 0.774) | | |

Statistical analyses

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|----------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 12 |
|----------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, sex, and age; LOCF. For the treatment comparison, results were presented for 29 subjects.

| | |
|---|--------------------------------|
| Comparison groups | Control Arm v Somatropin |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.364 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.37 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.21 |
| upper limit | 0.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.405 |

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, sex, and age; LOCF. For the treatment comparison, results are presented for 30 subjects.

| | |
|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.506 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | 0.48 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.345 |

Secondary: Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Suprailiac

| | |
|-----------------|--|
| End point title | Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Suprailiac |
|-----------------|--|

End point description:

Body composition measured as suprailiac skinfold thickness in mm; measured just above the iliac crest in the middle-axillary line. FAS; Control group received Somatropin from Month 12 onwards. Here n signifies the number of subjects evaluable at specific time point.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: millimeter(s) | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n=14, 12) | 0.51 (± 0.783) | 0.45 (± 0.849) | | |
| Month 24 (n=15, 12) | 0.9 (± 0.688) | 0.79 (± 0.774) | | |

Statistical analyses

| Statistical analysis title | Treatment difference Month 12 |
|--|--------------------------------|
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, sex, and age; LOCF. For the treatment comparison, results were presented for 26 subjects. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.959 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.42 |
| upper limit | 2.54 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.188 |

| Statistical analysis title | Treatment difference Month 24 |
|--|--------------------------------|
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, sex, and age; LOCF. For the treatment comparison, results were presented for 27 subjects. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.919 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.11 |
| upper limit | 2.32 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.065 |

Secondary: Change From Baseline in Volumetric Cortical Bone Mineral Density (BMD) Using Peripheral Quantitative Computed Tomography (pQCT) After 1 Year and After 2 Years

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|-----------------|--|
| End point title | Change From Baseline in Volumetric Cortical Bone Mineral Density (BMD) Using Peripheral Quantitative Computed Tomography (pQCT) After 1 Year and After 2 Years |
|-----------------|--|

End point description:

Volumetric Cortical BMD measured as milligrams per cubic millimeter (mg/mm³). BMD (proximal radius) SDS (number of standard deviations a subject's BMD differs from the average BMD of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score ($\ln[\text{test result}/M]/S$); \ln =natural logarithm; M =age- or height- and sex-specific mean value; S =age-(or height-) and sex-specific coefficient of variation then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: z-score | | | | |
| least squares mean (standard error) | | | | |
| month 12 (n=2, 6) | -1.055 (\pm 0.6802) | -0.162 (\pm 0.36) | | |
| Month 24(n=2, 6) | 0.284 (\pm 0.5023) | -0.433 (\pm 0.2658) | | |

Statistical analyses

| | |
|----------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 12 |
|----------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline volumetric cortical bone mineral density SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

| | |
|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.336 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.892 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.158 |
| upper limit | 1.374 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8161 |

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline volumetric cortical bone mineral density SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

| | |
|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.717 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.956 |
| upper limit | 2.391 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.6027 |

Secondary: Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Cortical Cross-sectional Area (CSA)

| | |
|-----------------|---|
| End point title | Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Cortical Cross-sectional Area (CSA) |
|-----------------|---|

End point description:

Bone structure Cortical CSA measured as millimeters squared (mm²). CSA (proximal radius) SDS (number of standard deviations a subject's CSA differs from the average CSA of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score ($\ln(\text{test result}/M)/S$); Ln=natural logarithm; M=age- or height-) and sex-specific mean value; S=age-(or height-) and sex-specific coefficient of variation) then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; n=number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: z-score | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n=2, 5) | -0.465 (± 0.7799) | 0.017 (± 0.4559) | | |
| Month 24 (n=2, 6) | -0.595 (± 0.7462) | 0.609 (± 0.3907) | | |

Statistical analyses

| Statistical analysis title | Treatment difference Month 12 |
|--|--------------------------------|
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline cortical cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results are presented for 7 subjects. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.653 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.482 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.558 |
| upper limit | 2.595 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.9666 |

| Statistical analysis title | Treatment difference Month 24 |
|--|--------------------------------|
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline cortical cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results are presented for 8 subjects. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.251 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.205 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.701 |
| upper limit | 1.292 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8991 |

Secondary: Change From Baseline in Bone Structure Using Peripheral Quantitative Computed Tomography (pQCT) After 1 Year and 2 Years: Total Cross-sectional Area (CSA)

| | |
|-----------------|--|
| End point title | Change From Baseline in Bone Structure Using Peripheral Quantitative Computed Tomography (pQCT) After 1 Year and 2 Years: Total Cross-sectional Area (CSA) |
|-----------------|--|

End point description:

Bone structure Total CSA measured as millimeters squared (mm²). Total CSA (proximal radius) SDS (number of standard deviations a subject's CSA differs from the average CSA of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score ($\ln[\text{test result}/M] / S$); \ln =natural logarithm; M = age- or height- and sex-specific mean value; S = age-(or height-) and sex-specific coefficient of variation then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: z-score | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n=2, 5) | 0.375 (± 0.9345) | 0.239 (± 0.5537) | | |
| Month 24 (n=2, 6) | 0.243 (± 0.3694) | -0.049 (± 0.1955) | | |

Statistical analyses

| | |
|----------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 12 |
|----------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline total cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 7 subjects.

| | |
|-------------------|--------------------------|
| Comparison groups | Somatropin v Control Arm |
|-------------------|--------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.914 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.135 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.524 |
| upper limit | 3.795 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.1499 |

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline total cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

| | |
|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.547 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.292 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.939 |
| upper limit | 1.522 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4432 |

Secondary: Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Muscle Cross-sectional Area (CSA)

| | |
|-----------------|---|
| End point title | Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Muscle Cross-sectional Area (CSA) |
|-----------------|---|

End point description:

Bone structure Muscle CSA measured as millimeters squared (mm²). CSA (proximal radius) SDS (number of standard deviations a subject's CSA differs from the average CSA of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score ($\ln [\text{test result}/M] / S$); \ln =natural logarithm; M = age- or height- and sex-specific mean value; S= age-(or height-) and sex-specific coefficient of variation then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: z-score | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n=2, 6) | 2.084 (± 0.3628) | -0.227 (± 0.1688) | | |
| Month 24 (n=2, 6) | 2.402 (± 0.5221) | 0.776 (± 0.2428) | | |

Statistical analyses

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 12 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline muscle cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

| | |
|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.007 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.049 |
| upper limit | 3.572 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4542 |

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline muscle cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

| | |
|-------------------|--------------------------|
| Comparison groups | Somatropin v Control Arm |
|-------------------|--------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.068 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.626 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.189 |
| upper limit | 3.44 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.6536 |

Secondary: Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Cortical Thickness (CT)

| | |
|---|---|
| End point title | Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Cortical Thickness (CT) |
| End point description: | |
| Cortical Thickness measured as millimeters (mm). CT (proximal radius) SDS (number of standard deviations a subject's CT differs from the average CT of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score ($\ln(\text{test result}/M)/S$); \ln = natural logarithm; M = age- or height-) and sex-specific mean value; S = age-(or height-) and sex-specific coefficient of variation) then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards. Cortical thickness was not analyzed as planned. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Month 12, Month 24 | |

| End point values | Somatropin | Control Arm | | |
|---|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | | |
| Units: z-score | | | | |
| least squares mean (standard deviation) | () | () | | |

Notes:

[1] - Cortical thickness was not analyzed as planned.

[2] - Cortical thickness was not analyzed as planned.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Marrow Area (MA)

| | |
|-----------------|--|
| End point title | Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Marrow Area (MA) |
|-----------------|--|

End point description:

Marrow Area measured as millimeters squared (mm^2). MA (proximal radius) SDS (number of standard deviations a subject's MA differs from the average MA of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score ($\ln(\text{test result}/M)/S$); \ln =natural logarithm; M =age- or height-) and sex-specific mean value; S = age-(or height-) and sex-specific coefficient of variation) then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards. Marrow Area was not analyzed as planned.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | | |
| Units: z-score | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[3] - Marrow Area was not analyzed as planned.

[4] - Marrow Area was not analyzed as planned.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Stability Using pQCT After 1 Year and After 2 Years: Strength-strain Index (SSI)

| | |
|-----------------|---|
| End point title | Change From Baseline in Bone Stability Using pQCT After 1 Year and After 2 Years: Strength-strain Index (SSI) |
|-----------------|---|

End point description:

Bone stability expressed as polar SSI in cubic millimeters (mm^3). SSI (proximal radius) SDS (number of standard deviations a subject's SSI differs from the average SSI of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score ($\ln[\text{test result}/M] / S$); \ln =natural logarithm; M =age- or height- and sex-specific mean value; S =age-(or height-) and sex-specific coefficient of variation then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: z-score | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n=2, 6) | 0.648 (\pm 0.4224) | 0.088 (\pm 0.2243) | | |

| | | | | |
|-------------------|-----------------------|-----------------------|--|--|
| Month 24 (n=2, 6) | 0.477 (\pm 0.3925) | 0.363 (\pm 0.2084) | | |
|-------------------|-----------------------|-----------------------|--|--|

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Treatment difference Month 12 |
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline strength-strain index SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.331 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.846 |
| upper limit | 1.965 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5061 |

| | |
|---|--------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
| Statistical analysis description: | |
| Results from ANCOVA adjusted for baseline strength-strain index SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects. | |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.82 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.114 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.192 |
| upper limit | 1.42 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4703 |

Secondary: Change From Baseline in Muscle Strength: Hand Grip SDS After 1 Year and After 2 Years

| | |
|-----------------|---|
| End point title | Change From Baseline in Muscle Strength: Hand Grip SDS After 1 Year and After 2 Years |
|-----------------|---|

End point description:

Muscle strength determined by measuring grip force (kilograms) using hand grip dynamometer for subjects ≥ 6 years of age. Baseline and post-baseline SDS values transformed to age and sex specific z-score. Change in hand grip calculated as SDS where $SDS = \text{hand grip} - \text{mean (age- and sex-matched reference)} / \text{SD (age- and sex-matched reference)}$. Positive values are above the average for subjects age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies the number of subjects ≥ 6 years of age with evaluable data at observation for Somatropin and Control Arm, respectively. SDS reference values used were for the right hand but the hand grip strength measured for this study was for the dominant hand (may not have been the right hand).

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

End point timeframe:

Baseline, Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: z-score | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n=7, 5) | 0.37 (\pm 0.268) | 0.28 (\pm 0.318) | | |
| Month 24 (n=7, 6) | 1.14 (\pm 0.218) | 0.92 (\pm 0.236) | | |

Statistical analyses

| | |
|----------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 12 |
|----------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline hand grip strength SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 12 subjects.

| | |
|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.844 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.88 |
| upper limit | 1.05 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.42 |

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Results from ANCOVA adjusted for baseline hand grip strength SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 13 subjects.

| | |
|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.519 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.52 |
| upper limit | 0.96 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.329 |

Secondary: Number of Subjects With Change in Insulin Sensitivity: Somatropin

| | |
|-----------------|--|
| End point title | Number of Subjects With Change in Insulin Sensitivity: Somatropin ^[5] |
|-----------------|--|

End point description:

Insulin sensitivity calculated as incidence of pathological glucose intolerance assessed prior to randomization (Screening Day -3 to Baseline Day 0) and at final visit (final visit: Somatropin treatment group = Month 24). Pathological glucose intolerance (oral glucose tolerance test) measured as venous (blood or plasma) with range minimum 120 milligrams per deciliter (mg/dL) to >140 mg/dL; capillary (blood) with range minimum 120 mg/dL to >120 mg/dL; or method not known with range minimum 120 mg/dL to >120 mg/dL. FAS population was analyzed for the endpoint.

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

End point timeframe:

Baseline, Month 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Comparison between groups was not planned. Data was not collected at Month 24 for Control Arm.

| End point values | Somatropin | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: subjects | | | | |
| Baseline: tolerant | 18 | | | |
| Baseline: intolerant | 0 | | | |
| Month 24: tolerant | 16 | | | |

| | | | | |
|----------------------|---|--|--|--|
| Month 24: intolerant | 0 | | | |
|----------------------|---|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Insulin Sensitivity: Control Arm

| | |
|-----------------|---|
| End point title | Number of Subjects With Change in Insulin Sensitivity: Control Arm ^[6] |
|-----------------|---|

End point description:

Insulin sensitivity calculated as incidence of pathological glucose intolerance assessed prior to randomization (Screening Day -3 to Baseline Day 0) and at final visit (final visit: Control Arm=Month 36). Pathological glucose intolerance (oral glucose tolerance test) measured as venous (blood or plasma) with range minimum 120 milligrams per deciliter (mg/dL) to >140 mg/dL; capillary (blood) with range minimum 120 mg/dL to >120 mg/dL; or method not known with range minimum 120 mg/dL to >120 mg/dL. FAS; Control group received Somatropin from Month 12 onwards.

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

End point timeframe:

Baseline, Month 36

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: comparison between groups was not planned. Data was not collected at Month 36 for Somatropin group.

| End point values | Control Arm | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 15 | | | |
| Units: subjects | | | | |
| Baseline: tolerant | 14 | | | |
| Baseline: intolerant | 1 | | | |
| Month 36: tolerant | 11 | | | |
| Month 36: intolerant | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Curve Comparison Based on Height SDS

| | |
|-----------------|---|
| End point title | Growth Curve Comparison Based on Height SDS |
|-----------------|---|

End point description:

Growth curve comparison with height SDS in centimeters as the dependent variable; SDS = height minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). FAS; Control group received Somatropin from Month 12 onwards. Data for Month 36 (applicable only to the Control Arm) is reported in a separate outcome measure. Here n signifies the number of subjects evaluable at specific time point.

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

End point timeframe:

Month 12, Month 24

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: centimeters | | | | |
| least squares mean (standard error) | | | | |
| Month 12 (n=18, 15) | -2.26 (\pm 0.0735) | -3.259 (\pm 0.0802) | | |
| Month 24 (n=18, 14) | -1.638 (\pm 0.1016) | -2.327 (\pm 0.1122) | | |

Statistical analyses

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 12 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Results from repeated measures mixed models analysis adjusted for baseline height SDS, visit, visit*treatment and target height SDS.

| | |
|---|--------------------------------|
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.998 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.778 |
| upper limit | 1.219 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1095 |

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Treatment difference Month 24 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Results from repeated measures mixed models analysis adjusted for baseline height SDS, visit, visit*treatment and target height SDS. For the treatment comparison, results were presented for 32 Subjects.

| | |
|-------------------|--------------------------|
| Comparison groups | Somatropin v Control Arm |
|-------------------|--------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.688 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.382 |
| upper limit | 0.994 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1519 |

Secondary: Growth Curve Comparison Based on Height SDS: Control Arm

| | |
|-----------------|--|
| End point title | Growth Curve Comparison Based on Height SDS: Control |
|-----------------|--|

End point description:

Growth curve comparison with height SDS in centimeters as the dependent variable; SDS = height minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). Control Arm final visit = Month 36. FAS; Control group received Somatropin from Month 12 onwards. Month 36 visit not applicable to Somatropin treatment group.

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

End point timeframe:

Month 36

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Comparison between groups was not planned at Month 36. No data was available for Somatropin group at Month 36.

| End point values | Control Arm | | | |
|-------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[8] | | | |
| Units: centimeters | | | | |
| least squares mean (standard error) | -1.794 (± 0.1318) | | | |

Notes:

[8] - N=number of subjects with evaluable data at observation.

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Curve Comparison Based on Height

| | |
|-----------------|---|
| End point title | Growth Curve Comparison Based on Height |
|-----------------|---|

End point description:

Growth curve comparison with height in centimeters as the dependent variable. FAS; Control group received Somatropin from Month 12 onwards. Data for Month 36 (applicable only to the Control Arm) is reported in a separate outcome measure. Here n signifies the number of subjects evaluable at specific

time point.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Month 12, Month 24 | |

| End point values | Somatropin | Control Arm | | |
|-------------------------------------|------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: centimeters | | | | |
| least squares mean (standard error) | | | | |
| Month 12 | 114.228 (\pm 0.333) | 109.644 (\pm 0.3733) | | |
| Month 24 | 123.351 (\pm 0.483) | 119.788 (\pm 0.5255) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment difference Month 12 |
| Statistical analysis description: | |
| | Results from repeated measure mixed models analysis adjusted for baseline height, sex, age, visit, visit*treatment and target height SDS. |
| Comparison groups | Somatropin v Control Arm |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.585 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.806 |
| upper limit | 5.363 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3859 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Treatment difference Month 24 |
| Statistical analysis description: | |
| | Results from repeated measure mixed models analysis adjusted for baseline height, sex, age, visit, visit*treatment and target height SDS. For the treatment comparison, results were presented for 32 subjects. |
| Comparison groups | Somatropin v Control Arm |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.563 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.134 |
| upper limit | 4.992 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.708 |

Secondary: Growth curve comparison with height in centimeters as the dependent variable.

| | |
|-----------------|--|
| End point title | Growth curve comparison with height in centimeters as the dependent variable. ^[9] |
|-----------------|--|

End point description:

Growth curve comparison with height in centimeters as the dependent variable. FAS; Control group received Somatropin from Month 12 onwards. Month 36 visit not applicable to Somatropin treatment group.

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

End point timeframe:

Month 36

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Comparison between groups was not planned at Month 36. No data was available for Somatropin group at Month 36.

| | | | | |
|-------------------------------------|--------------------|--|--|--|
| End point values | Control Arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[10] | | | |
| Units: centimeters | | | | |
| least squares mean (standard error) | 128.049 (± 0.7821) | | | |

Notes:

[10] - N = number of subjects with evaluable data at observation.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose of study treatment.

Adverse event reporting additional description:

Safety population=who received at least 1 dose of treatment. Same event may appear as AE, SAE. Distinct events are presented. Event may be categorized as serious in 1 subject, nonserious in another/subject may have experienced both serious, nonserious event during study. EU BR AE tables were generated as per EU format using latest coding dictionary.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Somatropin |
|-----------------------|------------|

Reporting group description:

The children were randomized into a treated group receiving 0.068 mg/kg/day (0.48 mg/kg/week) subcutaneous somatropin according to exact body weight specific calculation. Dose adjustments were made at 6 month intervals.

| | |
|-----------------------|-------------|
| Reporting group title | Control Arm |
|-----------------------|-------------|

Reporting group description:

The children were randomized into control group and after 1 year underwent Growth Hormone (GH) therapy, with 0.068 mg/kg/day (0.48mg/kg/week) subcutaneous somatropin according to exact body weight specific calculation. Dose adjustments were made at 6 month intervals.

| Serious adverse events | Somatropin | Control Arm | |
|--|-----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 18 (27.78%) | 1 / 15 (6.67%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Febrile convulsion | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 15 (6.67%) | |
| 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 | | | |
| Pyrexia | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis viral | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 0 / 15 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Somatropin | Control Arm | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 13 / 18 (72.22%) | 11 / 15 (73.33%) | |
| Injury, poisoning and procedural complications Wound subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 15 (0.00%) 0 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 2 | 1 / 15 (6.67%) 1 | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 15 (6.67%) 1 | |
| Eye disorders Visual impairment subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 15 (6.67%) 1 | |
| Gastrointestinal disorders Inguinal hernia subjects affected / exposed occurrences (all) Tooth disorder subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 1 / 18 (5.56%) 2 | 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 2 | 0 / 15 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 15 (0.00%) 0 | |
| Psychiatric disorders Attention deficit/hyperactivity disorder | | | |

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | 0 / 15 (0.00%) 0 | |
| Endocrine disorders | | | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 15 (6.67%) | |
| occurrences (all) | 0 | 1 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 15 (6.67%) | |
| occurrences (all) | 1 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 15 (6.67%) | |
| occurrences (all) | 0 | 1 | |
| Arthritis allergic | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nuchal rigidity | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Scoliosis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 15 (6.67%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 2 / 15 (13.33%) | |
| occurrences (all) | 3 | 3 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 2 / 15 (13.33%) | |
| occurrences (all) | 1 | 3 | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erythema infectiosum | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 15 (6.67%) | |
| occurrences (all) | 0 | 1 | |
| Febrile infection | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 18 (11.11%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 0 |
| Gastroenteritis | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 1 |
| Gastrointestinal infection | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nasopharyngitis | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 2 / 15 (13.33%) |
| occurrences (all) | 2 | 4 |
| Oral herpes | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 |
| Otitis media | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 15 (6.67%) |
| occurrences (all) | 6 | 1 |
| Otitis media acute | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 2 |
| Pharyngitis | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pneumonia | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rhinitis | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 1 / 15 (6.67%) |
| occurrences (all) | 3 | 1 |
| Scarlet fever | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 1 |
| Sinusitis | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 15 (0.00%) |
| occurrences (all) | 1 | 0 |
| Tonsillitis | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 18 (22.22%) 4 | 1 / 15 (6.67%) 1 | |
| Tooth abscess subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 15 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 4 | 2 / 15 (13.33%) 4 | |
| Varicella subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 15 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 24 January 2005 | Amendment was made to specific study procedures, subject selection and laboratory assessments. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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|--|
| Result values for the primary outcome measures were revised at the final analysis due to programmatic corrections: age rounded up if >6 months past last birthday. Height and height SDS not rounded for final analysis; rounded only for the reports. |
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Notes: