



## Clinical trial results:

### A two-year multi-centre, randomized two arm study of Genotropin treatment in very young children born small for gestational age: Early Growth and Neurodevelopment (EGN)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2007-003949-32                |
| Trial protocol           | SE CZ BE ES AT GB FR IT DE NL |
| Global end of trial date | 30 December 2013              |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 13 June 2016 |
| First version publication date | 25 July 2015 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A6281287 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00627523 |
| 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., 001-800 718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001-800 718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 23 May 2014      |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 December 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the effect of 24 months of treatment with growth hormone (GH) therapy at a dose of 0.035 milligram per kilogram per day (mg/kg/d) on height in short small for gestational age (SGA) children starting treatment at 24-30 months of age, compared to untreated controls, in randomized subjects.

Protection of trial subjects:

The study was in compliance with with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (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                          | 26 February 2008 |
| 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 | Netherlands: 1    |
| Country: Number of subjects enrolled | Spain: 15         |
| Country: Number of subjects enrolled | Sweden: 2         |
| Country: Number of subjects enrolled | Belgium: 5        |
| Country: Number of subjects enrolled | Czech Republic: 6 |
| Country: Number of subjects enrolled | Germany: 3        |
| Country: Number of subjects enrolled | Italy: 5          |
| Country: Number of subjects enrolled | Switzerland: 6    |
| Worldwide total number of subjects   | 43                |
| EEA total number of subjects         | 37                |

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          | 18 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 25 |
| 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:

This randomized controlled trial enrolled small for gestational age (SGA) children at 16 centers in 8 countries. In total, 52 subjects were screened for the study, of these, 9 subjects were considered screen failures. The remaining 43 subjects were randomized to receive either study drug (Genotropin) or were not treated (Control).

### Pre-assignment

Screening details:

Subjects aged between 19 to 29 months at Screening visit, born SGA (birth length and/or weight less than (<) 2 standard deviations (SD) for gestational age, using country specific standards), height below -2.5 SD at Screening (19-29 months of age), and had at least one measurement of length between 12 and 18 months of age were enrolled in this study

### Period 1

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

### Arms

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

Arm description:

Subjects received Genotropin at a dose of 0.035 mg/kg/d for 24 months. The dose was calculated based on the actual body weight, and the closest dosing step of the 5 mg pen used. The starting dose for the first 2 weeks was 1/3 of the calculated dose. After 2 weeks the dose was increased to 2/3 of the calculated dose. After 4 weeks the daily dose was the dose calculated on body weight at randomization.

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

Dosage and administration details:

Genotropin at a dose of 0.035 mg/kg/d for 24 months.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Control |
|------------------|---------|

Arm description:

This group was the untreated control group and was not administered placebo.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| Number of subjects in period 1 | Genotropin | Control |
|--------------------------------|------------|---------|
| Started                        | 21         | 22      |
| Completed                      | 19         | 20      |
| Not completed                  | 2          | 2       |
| 'Not specified '               | 1          | -       |
| Withdrawal by Subject          | -          | 2       |

|                  |   |   |
|------------------|---|---|
| Lack of efficacy | 1 | - |
|------------------|---|---|

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Genotropin |
|-----------------------|------------|

Reporting group description:

Subjects received Genotropin at a dose of 0.035 mg/kg/d for 24 months. The dose was calculated based on the actual body weight, and the closest dosing step of the 5 mg pen used. The starting dose for the first 2 weeks was 1/3 of the calculated dose. After 2 weeks the dose was increased to 2/3 of the calculated dose. After 4 weeks the daily dose was the dose calculated on body weight at randomization.

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

Reporting group description:

This group was the untreated control group and was not administered placebo.

| Reporting group values | Genotropin | Control | Total |
|------------------------|------------|---------|-------|
| Number of subjects     | 21         | 22      | 43    |
| Age categorical        |            |         |       |
| Units: Subjects        |            |         |       |
| Age continuous         |            |         |       |
| Units: months          |            |         |       |
| arithmetic mean        | 24.91      | 24.44   |       |
| standard deviation     | ± 3.262    | ± 3.324 | -     |
| Gender categorical     |            |         |       |
| Units: Subjects        |            |         |       |
| Female                 | 13         | 11      | 24    |
| Male                   | 8          | 11      | 19    |

## End points

### End points reporting groups

|   |            |
|---|------------|
| Reporting group title   | Genotropin |
| Reporting group description:  |            |
| Subjects received Genotropin at a dose of 0.035 mg/kg/d for 24 months. The dose was calculated based on the actual body weight, and the closest dosing step of the 5 mg pen used. The starting dose for the first 2 weeks was 1/3 of the calculated dose. After 2 weeks the dose was increased to 2/3 of the calculated dose. After 4 weeks the daily dose was the dose calculated on body weight at randomization. |            |
| Reporting group title   | Control    |
| Reporting group description:  |            |
| This group was the untreated control group and was not administered placebo.  |            |

### Primary: Change From Baseline in Height Standard Deviation Score (SDS) at Month 24

|   |   |
|---|---|
| End point title   | Change From Baseline in Height Standard Deviation Score (SDS) at Month 24 |
| End point description:  |   |
| Height SDS was calculated at the relevant visit by means of the following formula: Height SDS = (subject height) - (normal height) / normal height standard deviation. Where subject height refers to the subject's height at the relevant visit, and normal height and the normal height standard deviation equals the population mean and standard deviation values for subjects of a similar age and gender. The change from Baseline value for height SDS was calculated as the difference between the parameter values at a specific visit, and the Baseline parameter values. The scores were centred around 0. Negative score indicated a subject was smaller for their age/gender. Full Analysis Set (FAS) included subjects who were randomized to treatment and completed at least 1 post-baseline efficacy measure. Missing values were imputed using LOCF method. One subject was randomized to Genotropin but did not receive any treatment. This subject was excluded from FAS but included in Control for safety analysis. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| Baseline and Month 24   |   |

| End point values                    | Genotropin      | Control         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 21              | 21              |  |  |
| Units: SDS                          |                 |                 |  |  |
| least squares mean (standard error) | 1.63 (± 0.13)   | 0.43 (± 0.13)   |  |  |

### Statistical analyses

|  |                      |
|--|----------------------|
| Statistical analysis title   | Genotropin, Control  |
| Statistical analysis description:  |                      |
| The null hypothesis was that there was no difference in the mean change from Baseline after 24 months in height SDS between the Genotropin® and the untreated control groups. The alternative hypothesis was that there was a difference between the treatment groups. |                      |
| Comparison groups  | Genotropin v Control |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 42                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[1]</sup>     |
| P-value                                 | < 0.001                        |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1.2                            |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.82                           |
| upper limit                             | 1.59                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.19                           |

Notes:

[1] - Analysis of covariance (ANCOVA) model, fitting treatment as a factor, and the baseline parameter value as covariate was used. All hypotheses were tested at a 5% level of significance. No adjustments were made for multiple comparisons.

## Secondary: Change From Baseline in Growth Velocity SDS at Month 24

|                        |   |
|------------------------|---|
| End point title        | Change From Baseline in Growth Velocity SDS at Month 24   |
| End point description: | The growth velocity SDS was calculated at the relevant visit by means of the following formula: Growth velocity SDS = (subject growth velocity) - (normal growth velocity)/normal growth velocity standard deviation. Where, subject growth velocity refers to the subject's growth velocity at the relevant visit, and normal growth velocity and the normal growth velocity standard deviation equals the population mean and standard deviation values for subjects of a similar age and gender. The change from baseline value for growth velocity SDS was calculated as the difference between the parameter values at a specific visit, and the Baseline parameter values. FAS included subjects who were randomized to treatment and completed at least one post-baseline efficacy measure. Missing values were imputed using LOCF method. 1 subject was randomized to Genotropin but did not receive any treatment. This subject was excluded from FAS but included in Control for safety analysis. |
| End point type         | Secondary   |
| End point timeframe:   | Baseline and Month 24   |

| End point values                    | Genotropin      | Control         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 21              | 21              |  |  |
| Units: SDS                          |                 |                 |  |  |
| least squares mean (standard error) | 0.74 (± 0.57)   | -0.03 (± 0.57)  |  |  |

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| Statistical analysis title        | Genotropin®, Control   |
| Statistical analysis description: | The null hypothesis was that there was no difference between the Genotropin® and the untreated control group in terms of the relevant secondary endpoints. The alternative hypothesis was that a difference existed. |
| Comparison groups                 | Genotropin v Control   |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 42                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[2]</sup>     |
| P-value                                 | = 0.348                        |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.77                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.87                          |
| upper limit                             | 2.42                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.81                           |

Notes:

[2] - ANCOVA model, fitting treatment as a factor, and the baseline parameter value as covariate was used. All hypotheses were tested at a 5% level of significance. No adjustments were made for multiple comparisons.

## Secondary: Change From Baseline in Height SDS at Month 12

|                        |  |
|------------------------|--|
| End point title        | Change From Baseline in Height SDS at Month 12   |
| End point description: | Height SDS was calculated at the relevant visit by means of the following formula: Height SDS = (subject height) - (normal height)/normal height standard deviation. Where subject height refers to the subject's height at the relevant visit, and normal height and the normal height standard deviation equals the population mean and standard deviation values for subjects of a similar age and gender. The change from baseline value for height SDS was calculated as the difference between the parameter values at a specific visit, and the baseline parameter values. FAS included subjects who were randomized to treatment and completed at least one post-baseline efficacy measure. Missing values were imputed using LOCF method. 1 subject was randomized to Genotropin but did not receive any treatment. This subject was excluded from FAS but included in Control for safety analysis. |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline and month 12  |  |

| End point values                    | Genotropin      | Control         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 21              | 21              |  |  |
| Units: SDS                          |                 |                 |  |  |
| least squares mean (standard error) | 1.03 (± 0.12)   | 0.14 (± 0.12)   |  |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| Statistical analysis title        | Genotropin, Control   |
| Statistical analysis description: | The null hypothesis was that there was no difference between the Genotropin and the untreated control group in terms of the relevant secondary endpoints. The alternative hypothesis was that a difference existed. |
| Comparison groups                 | Genotropin v Control  |

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 42                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority <sup>[3]</sup>       |
| P-value                                 | < 0.001                          |
| Method                                  | ANCOVA                           |
| Parameter estimate                      | Median difference (final values) |
| Point estimate                          | 0.89                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.55                             |
| upper limit                             | 1.23                             |
| Variability estimate                    | Standard error of the mean       |
| Dispersion value                        | 0.17                             |

Notes:

[3] - ANCOVA model, fitting treatment as a factor, and the baseline parameter value as covariate was used. All hypotheses were tested at a 5% level of significance. No adjustments were made for multiple comparisons.

## Secondary: Change From Baseline in Growth Velocity SDS at Month 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Growth Velocity SDS at Month 12 |
|-----------------|---|

End point description:

The growth velocity SDS was calculated at the relevant visit by means of the following formula: Growth velocity SDS = (subject growth velocity) - (normal growth velocity)/normal growth velocity standard deviation. Where, subject growth velocity refers to the subject's growth velocity at the relevant visit, and normal growth velocity and the normal growth velocity standard deviation equals the population mean and standard deviation values for subjects of a similar age and gender. The change from Baseline value for growth velocity SDS was calculated as the difference between the parameter values at a specific visit, and the Baseline parameter values. FAS included subjects who were randomized to treatment and completed at least one post-baseline efficacy measure. Missing values were imputed using LOCF method. 1 subject was randomized to Genotropin® but did not receive any treatment. This subject was excluded from FAS but included in Control for safety analysis.

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

End point timeframe:

Baseline and Month 12

| End point values                    | Genotropin      | Control         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 21              | 21              |  |  |
| Units: SDS                          |                 |                 |  |  |
| least squares mean (standard error) | 1.65 (± 0.56)   | -1.59 (± 0.56)  |  |  |

## Statistical analyses

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Genotropin®, Control |
|----------------------------|----------------------|

Statistical analysis description:

The null hypothesis was that there was no difference between the Genotropin® and the untreated control group in terms of the relevant secondary endpoints. The alternative hypothesis was that a difference existed.

|                   |                      |
|-------------------|----------------------|
| Comparison groups | Genotropin v Control |
|-------------------|----------------------|

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 42                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[4]</sup>     |
| P-value                                 | < 0.001                        |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 3.24                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.63                           |
| upper limit                             | 4.85                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.8                            |

Notes:

[4] - ANCOVA model, fitting treatment as a factor, and the baseline parameter value as covariate was used. All hypotheses were tested at a 5% level of significance. No adjustments were made for multiple comparisons.

## Secondary: Change From Baseline in Mental Development Using the Mental Development Index (MDI) of Bayley Scale at Month 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Mental Development Using the Mental Development Index (MDI) of Bayley Scale at Month 12 |
|-----------------|---|

End point description:

The Bayley Scale of Infant Development (BSID-II) measured the mental and motor development and test behavior of subjects from 1 to 42 months of age. The scale was used to describe the current developmental functioning of infants and to assist in diagnosis and treatment planning for infants with developmental delays or disabilities. The BSID-II provided the mental raw score which was used to calculate the MDI score. Possible MDI scores ranged from 50-150. The MDI score of 69 and below indicated significantly delayed performance, 70 to 84 indicated mildly delayed performance, 85 to 114 indicated normal limit, and 115 and above indicated accelerated performance. FAS included subjects who were randomized to treatment and completed at least one post-baseline efficacy measure. One subject was randomized to Genotropin but did not receive any treatment. This subject was excluded from FAS but included in control group for safety analysis.

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

End point timeframe:

Baseline and month 12

| End point values                    | Genotropin      | Control         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 21              | 21              |  |  |
| Units: Units on a scale             |                 |                 |  |  |
| least squares mean (standard error) | 10.97 (± 5.34)  | 8.55 (± 4.74)   |  |  |

## Statistical analyses

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Genotropin®, Control |
|----------------------------|----------------------|

Statistical analysis description:

The null hypothesis was that there was no difference between the Genotropin® and the untreated control group in terms of the relevant secondary endpoints. The alternative hypothesis was that a

difference existed. ANCOVA model, fitting treatment as a factor, and the baseline parameter value, age, and gender as covariates were used. All hypotheses were tested at a 5% level of significance. No adjustments were made for multiple comparisons.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Genotropin v Control           |
| Number of subjects included in analysis | 42                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.738                        |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 2.43                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -12.27                         |
| upper limit                             | 17.12                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 7.19                           |

## Secondary: Change From Baseline in Psychomotor Development Using the Psychomotor Development Index (PDI) of Bayley Scale at Month 12

|                        |   |
|------------------------|---|
| End point title        | Change From Baseline in Psychomotor Development Using the Psychomotor Development Index (PDI) of Bayley Scale at Month 12   |
| End point description: | BSID-II measured the mental and motor development and test behavior of subjects from 1 to 42 months of age. The scale was used to describe the current developmental functioning of infants and to assist in diagnosis and treatment planning for infants with developmental delays or disabilities. The BSID-II provided the psychomotor raw score which was used to calculate the PDI score. The PDI score of 69 and below indicated significantly delayed performance, 70 to 84 indicated mildly delayed performance, 85 to 114 indicated normal limit, and 115 and above indicated accelerated performance. FAS included subjects who were randomized to treatment and completed at least one post-baseline efficacy measure. One subject was randomized to Genotropin but did not receive any treatment. This subject was excluded from FAS but included in Control group for safety analysis. |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline and Month 12  |   |

| End point values                    | Genotropin      | Control         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 21              | 21              |  |  |
| Units: Units on a scale             |                 |                 |  |  |
| least squares mean (standard error) | 4.04 (± 3.04)   | 8.55 (± 2.84)   |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>   | Genotropin, Control            |
| Statistical analysis description:   |                                |
| The null hypothesis was that there was no difference between the Genotropin and the untreated control group in terms of the relevant secondary endpoints. The alternative hypothesis was that a difference existed. |                                |
| Comparison groups   | Control v Genotropin           |
| Number of subjects included in analysis   | 42                             |
| Analysis specification  | Pre-specified                  |
| Analysis type   | superiority <sup>[5]</sup>     |
| P-value   | = 0.301                        |
| Method  | ANCOVA                         |
| Parameter estimate  | Mean difference (final values) |
| Point estimate  | -4.51                          |
| Confidence interval   |                                |
| level   | 95 %                           |
| sides   | 2-sided                        |
| lower limit   | -13.27                         |
| upper limit   | 4.26                           |
| Variability estimate  | Standard error of the mean     |
| Dispersion value  | 4.27                           |

Notes:

[5] - ANCOVA model, fitting treatment as a factor, and the baseline parameter value, age, and gender as covariates were used. All hypotheses were tested at a 5% level of significance. No adjustments were made for multiple comparisons.

### Secondary: Head Circumference SDS at Months 3, 6, 12, 18 and 24

|   |  |
|---|--|
| End point title   | Head Circumference SDS at Months 3, 6, 12, 18 and 24 |
| End point description:  |  |
| Head circumference SDS was calculated by means of the following formula = (Subject head circumference) - (Normal head circumference) / Normal head circumference standard deviation. Where subject head circumference refers to the subject's head circumference at the relevant visit, and normal head circumference and the normal head circumference standard deviation equals the population mean and standard deviation values for subjects of a similar age and gender. FAS included subjects who were randomized to treatment and completed at least one post-baseline efficacy measure. One subject was randomized to Genotropin but did not receive any treatment. This subject was excluded from FAS but included in Control group for safety analysis. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Months 3, 6, 12, 18 and 24  |  |

| End point values                     | Genotropin      | Control         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 21              | 21              |  |  |
| Units: SDS                           |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Month 3 (n = 21, 19)                 | -0.93 (± 1.217) | -1.37 (± 1.122) |  |  |
| Month 6 (n = 21, 19)                 | -1.2 (± 1.31)   | -1.72 (± 1.077) |  |  |
| Month 12 (n = 20, 18)                | -0.87 (± 1.33)  | -1.84 (± 1.158) |  |  |
| Month 18 (n = 20, 19)                | -0.56 (± 1.89)  | -1.76 (± 1.153) |  |  |

|                       |                 |                 |  |  |
|-----------------------|-----------------|-----------------|--|--|
| Month 24 (n = 20, 20) | -0.75 (± 1.384) | -1.65 (± 1.227) |  |  |
|-----------------------|-----------------|-----------------|--|--|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Head Circumference SDS at Months 3, 6, 12, 18 and 24

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Head Circumference SDS at Months 3, 6, 12, 18 and 24 |
|-----------------|--|

End point description:

Head circumference SDS was calculated by means of the following formula = (Subject head circumference)-(Normal head circumference)/Normal head circumference standard deviation. Where subject head circumference refers to the subject's head circumference at the relevant visit, and normal head circumference and the normal head circumference standard deviation equals the population mean and standard deviation values for subjects of a similar age and gender. FAS included subjects who were randomized to treatment and completed at least one post-baseline efficacy measure. One subject was randomized to Genotropin® but did not receive any treatment. This subject was excluded from FAS but included in Control group for safety analysis.

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

End point timeframe:

Baseline, Months 3, 6, 12, 18 and 24

| End point values                     | Genotropin      | Control         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 21              | 21              |  |  |
| Units: SDS                           |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Month 3 (n = 21, 19)                 | 0.27 (± 0.977)  | 0.36 (± 0.693)  |  |  |
| Month 6 (n = 21, 19)                 | 0 (± 0.423)     | 0.07 (± 0.495)  |  |  |
| Month 12 (n = 20, 18)                | 0.26 (± 0.516)  | 0.02 (± 0.587)  |  |  |
| Month 18 (n = 20, 19)                | 0.57 (± 1.094)  | 0.04 (± 0.506)  |  |  |
| Month 24 (n = 20, 20)                | 0.39 (± 0.638)  | 0.08 (± 0.602)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Body Weight at Months 3, 6, 12, 18, and 24

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Body Weight at Months 3, 6, 12, 18, and 24 |
|-----------------|--|

End point description:

Body weight was measured at all the relevant visits. The change from Baseline in body weight was calculated as the difference between the parameter values at each visit, and the Baseline parameter values. FAS included subjects who were randomized to treatment and completed at least one post-

baseline efficacy measure. One subject was randomized to Genotropin but did not receive any treatment. This subject was excluded from FAS but included in control group for safety analysis.

|                                       |           |
|---------------------------------------|-----------|
| End point type                        | Secondary |
| End point timeframe:                  |           |
| Baseline, Months 3, 6, 12, 18, and 24 |           |

| End point values                     | Genotropin      | Control         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 21              | 21              |  |  |
| Units: kilogram(s)                   |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Month 3 (n = 21, 19)                 | 0.57 (± 0.154)  | 0.53 (± 0.406)  |  |  |
| Month 6 (n = 21, 20)                 | 1.08 (± 0.269)  | 1.01 (± 0.659)  |  |  |
| Month 12 (n = 20, 19)                | 2.34 (± 0.389)  | 1.66 (± 0.397)  |  |  |
| Month 18 (n = 20, 19)                | 3.48 (± 0.669)  | 2.41 (± 0.709)  |  |  |
| Month 24 (n = 20, 20)                | 4.79 (± 0.814)  | 3.19 (± 0.601)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Body Mass Index (BMI) at Months 3, 6, 12, 18, and 24

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Body Mass Index (BMI) at Months 3, 6, 12, 18, and 24 |
|-----------------|--|

End point description:

BMI was calculated for all visits by means of the following formula: BMI Kilogram per meters square ( $\text{kg/m}^2$ ) = Weight Kilogram per height meters square ( $\text{kg}$ ) / ( $\text{Height[m]}^2$ ). The change from baseline BMI was calculated as the difference between the parameter values at each visit, and the baseline parameter values. FAS included subjects who were randomized to treatment and completed at least one post-baseline efficacy measure. One subject was randomized to Genotropin but did not receive any treatment. This subject was excluded from FAS but included in Control group for safety analysis.

|                                       |           |
|---------------------------------------|-----------|
| End point type                        | Secondary |
| End point timeframe:                  |           |
| Baseline, Months 3, 6, 12, 18, and 24 |           |

| End point values                     | Genotropin      | Control         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 21              | 21              |  |  |
| Units: Kilogram/meters <sup>2</sup>  |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Month 3 (n = 21, 19)                 | -0.28 (± 0.419) | -0.05 (± 0.811) |  |  |
| Month 6 (n = 21, 20)                 | -0.57 (± 0.537) | 0.08 (± 1.013)  |  |  |

|                       |                 |                 |  |  |
|-----------------------|-----------------|-----------------|--|--|
| Month 12 (n = 20, 19) | -0.62 (± 0.65)  | -0.29 (± 0.683) |  |  |
| Month 18 (n = 20, 19) | -0.78 (± 0.93)  | -0.25 (± 0.806) |  |  |
| Month 24 (n = 20, 20) | -0.58 (± 0.823) | -0.55 (± 0.776) |  |  |

## Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from screening (Visit 1) until the follow-up visit for subjects in both treatment groups.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | v16.1  |

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Genotropin |
|-----------------------|------------|

Reporting group description:

Subjects received Genotropin at a dose of 0.035 mg/kg/d for 24 months. The dose was calculated based on the actual body weight, and the closest dosing step of the 5 mg pen used. The starting dose for the first 2 weeks was 1/3 of the calculated dose. After 2 weeks the dose was increased to 2/3 of the calculated dose. After 4 weeks the daily dose was the dose calculated on body weight at randomization.

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

Reporting group description:

This group was the untreated control group and was not administered placebo.

| Serious adverse events                            | Genotropin      | Control        |  |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events |                 |                |  |
| subjects affected / exposed                       | 6 / 21 (28.57%) | 2 / 22 (9.09%) |  |
| number of deaths (all causes)                     | 0               | 0              |  |
| number of deaths resulting from adverse events    | 0               | 0              |  |
| Injury, poisoning and procedural complications    |                 |                |  |
| Concussion  |                 |                |  |
| subjects affected / exposed                       | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0          |  |
| Ear and labyrinth disorders                       |                 |                |  |
| Conductive deafness                               |                 |                |  |
| subjects affected / exposed                       | 2 / 21 (9.52%)  | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders   |                 |                |  |
| Adenoidal hypertrophy                             |                 |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Asthma  |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Tonsillar hypertrophy                           |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Bronchopneumonia                                |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastroenteritis                                 |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hordeolum                                       |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Rotavirus infection                             |                |                |  |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 1 / 22 (4.55%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Viral infection                                 |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Dehydration                                     |                |                |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (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: 4 %

| <b>Non-serious adverse events</b>                     | Genotropin        | Control          |  |
|---|-------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                   |                  |  |
| subjects affected / exposed                           | 21 / 21 (100.00%) | 18 / 22 (81.82%) |  |
| Vascular disorders                                    |                   |                  |  |
| Haematoma   |                   |                  |  |
| subjects affected / exposed                           | 2 / 21 (9.52%)    | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 2                 | 0                |  |
| General disorders and administration site conditions  |                   |                  |  |
| Injection site bruising                               |                   |                  |  |
| subjects affected / exposed                           | 1 / 21 (4.76%)    | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 1                 | 0                |  |
| Irritability  |                   |                  |  |
| subjects affected / exposed                           | 1 / 21 (4.76%)    | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 1                 | 0                |  |
| Pyrexia   |                   |                  |  |
| subjects affected / exposed                           | 9 / 21 (42.86%)   | 4 / 22 (18.18%)  |  |
| occurrences (all)                                     | 13                | 7                |  |
| Immune system disorders                               |                   |                  |  |
| Hypersensitivity                                      |                   |                  |  |
| subjects affected / exposed                           | 1 / 21 (4.76%)    | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 1                 | 0                |  |
| Milk allergy  |                   |                  |  |
| subjects affected / exposed                           | 0 / 21 (0.00%)    | 1 / 22 (4.55%)   |  |
| occurrences (all)                                     | 0                 | 1                |  |
| Respiratory, thoracic and mediastinal disorders       |                   |                  |  |
| Adenoidal hypertrophy                                 |                   |                  |  |
| subjects affected / exposed                           | 2 / 21 (9.52%)    | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 2                 | 0                |  |
| Asthma  |                   |                  |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| subjects affected / exposed                    | 1 / 21 (4.76%)  | 1 / 22 (4.55%) |  |
| occurrences (all)                              | 1               | 2              |  |
| Bronchial dysplasia                            |                 |                |  |
| subjects affected / exposed                    | 0 / 21 (0.00%)  | 1 / 22 (4.55%) |  |
| occurrences (all)                              | 0               | 1              |  |
| Cough  |                 |                |  |
| subjects affected / exposed                    | 3 / 21 (14.29%) | 1 / 22 (4.55%) |  |
| occurrences (all)                              | 5               | 1              |  |
| Increased bronchial secretion                  |                 |                |  |
| subjects affected / exposed                    | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |  |
| occurrences (all)                              | 1               | 0              |  |
| Respiratory disorder                           |                 |                |  |
| subjects affected / exposed                    | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |  |
| occurrences (all)                              | 1               | 0              |  |
| Rhinorrhoea                                    |                 |                |  |
| subjects affected / exposed                    | 2 / 21 (9.52%)  | 0 / 22 (0.00%) |  |
| occurrences (all)                              | 2               | 0              |  |
| Psychiatric disorders                          |                 |                |  |
| Insomnia                                       |                 |                |  |
| subjects affected / exposed                    | 2 / 21 (9.52%)  | 0 / 22 (0.00%) |  |
| occurrences (all)                              | 2               | 0              |  |
| Investigations                                 |                 |                |  |
| Alanine aminotransferase increased             |                 |                |  |
| subjects affected / exposed                    | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |  |
| occurrences (all)                              | 2               | 0              |  |
| Aspartate aminotransferase increased           |                 |                |  |
| subjects affected / exposed                    | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |  |
| occurrences (all)                              | 1               | 0              |  |
| Injury, poisoning and procedural complications |                 |                |  |
| Face injury                                    |                 |                |  |
| subjects affected / exposed                    | 0 / 21 (0.00%)  | 1 / 22 (4.55%) |  |
| occurrences (all)                              | 0               | 1              |  |
| Nervous system disorders                       |                 |                |  |
| Headache                                       |                 |                |  |
| subjects affected / exposed                    | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |  |
| occurrences (all)                              | 2               | 0              |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Syncope<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 21 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1  |  |
| Ear and labyrinth disorders<br>Ear disorder<br>subjects affected / exposed<br>occurrences (all)  | 1 / 21 (4.76%)<br>1  | 0 / 22 (0.00%)<br>0  |  |
| Tympanic membrane disorder<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 21 (4.76%)<br>1  | 0 / 22 (0.00%)<br>0  |  |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)              | 3 / 21 (14.29%)<br>3 | 2 / 22 (9.09%)<br>2  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 21 (9.52%)<br>2  | 0 / 22 (0.00%)<br>0  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 21 (4.76%)<br>1  | 1 / 22 (4.55%)<br>1  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                    | 4 / 21 (19.05%)<br>8 | 0 / 22 (0.00%)<br>0  |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 21 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1  |  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 21 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1  |  |
| Regurgitation<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 21 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 21 (19.05%)<br>6 | 4 / 22 (18.18%)<br>5 |  |
| Skin and subcutaneous tissue disorders   |                      |                      |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Acne  |                 |                 |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Dermatitis diaper                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Eczema  |                 |                 |  |
| subjects affected / exposed                     | 2 / 21 (9.52%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                               | 2               | 1               |  |
| Lipoatrophy                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 0 / 21 (0.00%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Growing pains                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)  | 0 / 22 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Infections and infestations                     |                 |                 |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 6 / 21 (28.57%) | 6 / 22 (27.27%) |  |
| occurrences (all)                               | 12              | 11              |  |
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 21 (0.00%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 21 (0.00%)  | 1 / 22 (4.55%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Ear infection                                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 21 (14.29%) | 1 / 22 (4.55%)  |  |
| occurrences (all)                               | 4               | 1               |  |
| Exanthema subitum                               |                 |                 |  |

|                                  |                 |                 |
|----------------------------------|-----------------|-----------------|
| subjects affected / exposed      | 2 / 21 (9.52%)  | 0 / 22 (0.00%)  |
| occurrences (all)                | 2               | 0               |
| Gastroenteritis                  |                 |                 |
| subjects affected / exposed      | 2 / 21 (9.52%)  | 2 / 22 (9.09%)  |
| occurrences (all)                | 3               | 2               |
| Gastroenteritis viral            |                 |                 |
| subjects affected / exposed      | 2 / 21 (9.52%)  | 0 / 22 (0.00%)  |
| occurrences (all)                | 3               | 0               |
| Gastrointestinal viral infection |                 |                 |
| subjects affected / exposed      | 0 / 21 (0.00%)  | 1 / 22 (4.55%)  |
| occurrences (all)                | 0               | 1               |
| Hordeolum                        |                 |                 |
| subjects affected / exposed      | 1 / 21 (4.76%)  | 0 / 22 (0.00%)  |
| occurrences (all)                | 1               | 0               |
| Influenza                        |                 |                 |
| subjects affected / exposed      | 1 / 21 (4.76%)  | 0 / 22 (0.00%)  |
| occurrences (all)                | 1               | 0               |
| Laryngitis                       |                 |                 |
| subjects affected / exposed      | 4 / 21 (19.05%) | 0 / 22 (0.00%)  |
| occurrences (all)                | 4               | 0               |
| Molluscum contagiosum            |                 |                 |
| subjects affected / exposed      | 0 / 21 (0.00%)  | 1 / 22 (4.55%)  |
| occurrences (all)                | 0               | 1               |
| Nasopharyngitis                  |                 |                 |
| subjects affected / exposed      | 9 / 21 (42.86%) | 6 / 22 (27.27%) |
| occurrences (all)                | 23              | 9               |
| Otitis media                     |                 |                 |
| subjects affected / exposed      | 3 / 21 (14.29%) | 1 / 22 (4.55%)  |
| occurrences (all)                | 5               | 1               |
| Otitis media acute               |                 |                 |
| subjects affected / exposed      | 1 / 21 (4.76%)  | 1 / 22 (4.55%)  |
| occurrences (all)                | 3               | 1               |
| Pharyngitis                      |                 |                 |
| subjects affected / exposed      | 2 / 21 (9.52%)  | 1 / 22 (4.55%)  |
| occurrences (all)                | 2               | 1               |
| Pharyngotonsillitis              |                 |                 |

|   |                 |                |
|---|-----------------|----------------|
| subjects affected / exposed             | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |
| occurrences (all)                       | 1               | 0              |
| Pneumonia                               |                 |                |
| subjects affected / exposed             | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |
| occurrences (all)                       | 1               | 0              |
| Respiratory tract infection             |                 |                |
| subjects affected / exposed             | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |
| occurrences (all)                       | 1               | 0              |
| Rhinitis                                |                 |                |
| subjects affected / exposed             | 2 / 21 (9.52%)  | 2 / 22 (9.09%) |
| occurrences (all)                       | 4               | 4              |
| Scarlet fever                           |                 |                |
| subjects affected / exposed             | 0 / 21 (0.00%)  | 1 / 22 (4.55%) |
| occurrences (all)                       | 0               | 1              |
| Tonsillitis                             |                 |                |
| subjects affected / exposed             | 2 / 21 (9.52%)  | 1 / 22 (4.55%) |
| occurrences (all)                       | 7               | 1              |
| Upper respiratory tract infection       |                 |                |
| subjects affected / exposed             | 8 / 21 (38.10%) | 1 / 22 (4.55%) |
| occurrences (all)                       | 23              | 5              |
| Varicella                               |                 |                |
| subjects affected / exposed             | 4 / 21 (19.05%) | 1 / 22 (4.55%) |
| occurrences (all)                       | 4               | 1              |
| Viral infection                         |                 |                |
| subjects affected / exposed             | 2 / 21 (9.52%)  | 0 / 22 (0.00%) |
| occurrences (all)                       | 3               | 0              |
| Viral upper respiratory tract infection |                 |                |
| subjects affected / exposed             | 1 / 21 (4.76%)  | 0 / 22 (0.00%) |
| occurrences (all)                       | 1               | 0              |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 21 November 2007 | Amended to include updated Pfizer standard wording for SAE reporting. |
| 22 February 2012 | Revision of safety and Hy's law sections.                             |
| 22 February 2012 | Revision of AE reporting.   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported