



Clinical trial results:

Multicentre study to evaluate the efficacy and safety of a liquid formulation of recombinant growth hormone, Omnitrope® 3.3mg/mL, in the treatment of pre-pubertal children of small stature suffering from somatotropin deficiency (GH) – phase IIIb

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-002802-34 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 31 July 2008 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 31 March 2016 |
| First version publication date | 31 March 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------------------|
| Sponsor protocol code | Sandoz/OMNI/F/01/03 |
|-----------------------|---------------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Sandoz S.A.S |
| Sponsor organisation address | 49, avenue Georges Pompidou, Levallois-Perret Cedex, France, 92300 |
| Public contact | Strategic Planning Biopharma Clinical Development, Sandoz, 0049 80244760, biopharma.cliniclatrials@sandoz.com |
| Scientific contact | Strategic Planning Biopharma Clinical Development, Sandoz, 0049 80244760, biopharma.cliniclatrials@sandoz.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 | 08 November 2011 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 July 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and tolerance of Omnitrope® 3.3 mg/ml injection, administered at a dose of 0.23 mg/kg/week, in terms of clinical and immunological parameters, and laboratory test results.

Protection of trial subjects:

Before the patient embarked on the study, the Investigator was obliged to explain clearly to every Patient/Family/Legal Representative the nature and objectives of the clinical trial, its benefits and risks, their rights and the confidentiality of the data, before providing a copy of the Information Sheet to read and keep.

At the Pre-Inclusion Visit, after the Patient/Family/Legal Representative had familiarised themselves with the information provided, the Investigator asked them to give their agreement in writing by dating page and signing the Informed Consent Form.

For the Amendments that entailed changes to the Information Sheet and Informed Consent Form, the Investigator had to get new Forms signed and dated by every Patient/Family/Legal Representative.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 20 October 2003 |
| 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 | France: 53 |
| Worldwide total number of subjects | 53 |
| EEA total number of subjects | 53 |

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) | 53 |
| 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:

A total of 100 patients should have been recruited in 41 French sites, due to slow recruitment 51 patients were enrolled in 23 sites
first patient first visit 20 Oct 2003
last patient first visit 13 Nov 2006
last patient last visit 31 Jul 2008.

Pre-assignment

Screening details:

53 patients were screened, 2 patients didn't meet the screening criteria and were therefore not included in the study due to either violation of inclusion criteria or growth hormone test not showing deficiency

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 53 |
| Number of subjects completed | 51 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-----------------------|
| Reason: Number of subjects | Protocol deviation: 2 |
|----------------------------|-----------------------|

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Treatment Phase up to Month 12 |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|------------------|
| Arm title | All patients |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Omnitrope® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Omnitrope® 3.3 mg/mL injection administered subcutaneously using an injector pen with ready-to-use 1.5 ml cartridges. Included patients were given a dosage of 0.23 mg/kg/week, i.e. 0.033 mg/kg/day injected once daily for 12 months.

| | |
|---|--------------|
| Number of subjects in period 1^[1] | All patients |
| Started | 51 |
| Completed | 51 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 2 patients were screened but not enrolled into the trial

Period 2

| | |
|------------------------------|-------------------------------|
| Period 2 title | Treatment Phase Month 12 - 24 |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

NAP

Arms

| | |
|------------------|--------------|
| Arm title | All patients |
|------------------|--------------|

Arm description:

This study phase was already voluntary for the patients. Therefore 51 started and only 41 ended it.

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

Dosage and administration details:

Omnitrope® 3.3 mg/mL injection administered subcutaneously using an injector pen with ready-to-use 1.5 ml cartridges. Included patients were given a dosage of 0.23 mg/kg/week, i.e. 0.033 mg/kg/day injected once daily for 12 months.

| Number of subjects in period 2 | All patients |
|----------------------------------|--------------|
| Started | 51 |
| Completed | 41 |
| Not completed | 10 |
| Consent withdrawn by subject | 1 |
| Unknown but no AE | 5 |
| Switch to commercialised product | 3 |
| Lack of efficacy | 1 |

Period 3

| | |
|------------------------------|-------------------------------|
| Period 3 title | Treatment Phase Month 24 - 36 |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

NAP

Arms

| | |
|--|------------------|
| Arm title | All patients |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Omnitrope® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Omnitrope® 3.3 mg/mL injection administered subcutaneously using an injector pen with ready-to-use 1.5 ml cartridges. Included patients were given a dosage of 0.23 mg/kg/week, i.e. 0.033 mg/kg/day injected once daily for 12 months.

| Number of subjects in period 3 | All patients |
|---------------------------------------|--------------|
| Started | 41 |
| Completed | 24 |
| Not completed | 17 |
| Unknown but no AE | 8 |
| Lost to follow-up | 2 |
| Switch to commercialised product | 4 |
| Lack of efficacy | 1 |
| Protocol deviation | 2 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|--------------------------------|
| Reporting group title | Treatment Phase up to Month 12 |
| Reporting group description: - | |

| Reporting group values | Treatment Phase up to Month 12 | Total | |
|---|--------------------------------|-------|--|
| Number of subjects | 51 | 51 | |
| Age categorical | | | |
| Patients where divided into 3 agegroup | | | |
| Units: Subjects | | | |
| < 4 years | 7 | 7 | |
| [4-8) years | 27 | 27 | |
| >= 8 years | 17 | 17 | |
| Age continuous | | | |
| children with the age of 1.19 to 11.62 years were included into the study | | | |
| Units: years | | | |
| arithmetic mean | 6.87 | | |
| full range (min-max) | 1.33 to 11.82 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | |
| Male | 42 | 42 | |
| Scan of brain | | | |
| MR examination of the brain, with centralised reading for the results | | | |
| Units: Subjects | | | |
| Normal | 1 | 1 | |
| Not done | 50 | 50 | |
| MRI brain | | | |
| Units: Subjects | | | |
| Normal | 20 | 20 | |
| Abnormal | 16 | 16 | |
| Not done | 15 | 15 | |
| Gestational Age [weeks] | | | |
| Units: weeks | | | |
| arithmetic mean | 39.22 | | |
| full range (min-max) | 34 to 46 | - | |
| Birth height | | | |
| Units: cm | | | |
| arithmetic mean | 47.96 | | |
| full range (min-max) | 42 to 51 | - | |
| Birth weight | | | |
| Units: gram(s) | | | |
| arithmetic mean | 3110 | | |
| full range (min-max) | 1420 to 4760 | - | |
| Cranial perimeter | | | |
| Units: cm | | | |
| arithmetic mean | 34.53 | | |

| | | | |
|--|----------------|---|--|
| full range (min-max) | 31 to 38.5 | - | |
| Father's height | | | |
| Units: cm | | | |
| arithmetic mean | 171.7 | | |
| full range (min-max) | 155 to 193.5 | - | |
| Age of father's puberty | | | |
| Units: years | | | |
| arithmetic mean | 14.11 | | |
| full range (min-max) | 12.6 to 17 | - | |
| Mother's height | | | |
| Units: cm | | | |
| arithmetic mean | 158.12 | | |
| full range (min-max) | 139.5 to 174 | - | |
| Age of mother's first menstruation | | | |
| Units: years | | | |
| arithmetic mean | 13.21 | | |
| full range (min-max) | 10.6 to 17 | - | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 17.91 | | |
| full range (min-max) | 8.3 to 34.5 | - | |
| BMI | | | |
| Units: kg/cm2 | | | |
| arithmetic mean | 15.35 | | |
| full range (min-max) | 12.12 to 25.38 | - | |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 106.49 | | |
| full range (min-max) | 73 to 134 | - | |
| Height SDS | | | |
| height minus standard height of the respective age divided by standard deviation for the respective age of the standard population | | | |
| Units: SDS | | | |
| arithmetic mean | -2.39 | | |
| full range (min-max) | -4.03 to -1.47 | - | |

End points

End points reporting groups

| | |
|---|--------------|
| Reporting group title | All patients |
| Reporting group description: - | |
| Reporting group title | All patients |
| Reporting group description: This study phase was already voluntary for the patients. Therefore 51 started and only 41 ended it. | |
| Reporting group title | All patients |
| Reporting group description: - | |

Primary: Height velocity after 12 months

| | |
|--|--|
| End point title | Height velocity after 12 months ^[1] |
| End point description: Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25. To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements. | |
| End point type | Primary |
| End point timeframe: 12 months | |

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| End point values | All patients | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 51 | | | |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height velocity month 12 | 9.66 (± 2.14) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height velocity after 24 months

| | |
|--|--|
| End point title | Height velocity after 24 months ^[2] |
| End point description: Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25. To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements. | |
| End point type | Primary |

End point timeframe:
Month 12 to month 24

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height velocity month 24 | 8.65 (± 1.42) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height velocity after 36 months

| | |
|-----------------|--|
| End point title | Height velocity after 36 months ^[3] |
|-----------------|--|

End point description:

Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25. To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.

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

End point timeframe:

Month 24 to 36

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height velocity month 36 | 8.2 (± 1) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height velocity SDS after 12 months

| | |
|-----------------|--|
| End point title | Height velocity SDS after 12 months ^[4] |
|-----------------|--|

End point description:

Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25.

Increase in height velocity SDS (related to chronological age and gender)

SDS values are calculated for height velocity using the following equation: $SDS = X1 - X2 / SD$ in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.

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

End point timeframe:

Baseline to month 12

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 51 | | | |
| Units: SDS/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height velocity SDS month 12 | 4.66 (± 3.07) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height velocity SDS after 24 months

| | |
|-----------------|--|
| End point title | Height velocity SDS after 24 months ^[5] |
|-----------------|--|

End point description:

Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25.

Increase in height velocity SDS (related to chronological age and gender)

SDS values are calculated for height velocity using the following equation: $SDS = X1 - X2 / SD$ in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.

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

End point timeframe:

month 12 to 24

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| End point values | All patients | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: SDS/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height velocity SDS month 24 | 3.45 (± 2.2) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height velocity SDS after 36 months

| | |
|-----------------|--|
| End point title | Height velocity SDS after 36 months ^[6] |
|-----------------|--|

End point description:

Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25.

Increase in height velocity SDS (related to chronological age and gender)

SDS values are calculated for height velocity using the following equation: $SDS = X1 - X2 / SD$ in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.

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

End point timeframe:

month 24 to 36

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| End point values | All patients | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: SDS/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height velocity SDS month 36 | 2.55 (± 2.01) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height gain after 12 months

| | |
|-----------------|--|
| End point title | Height gain after 12 months ^[7] |
|-----------------|--|

End point description:

Height gain expressed in cm

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

End point timeframe:

Baseline to month 12

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| End point values | All patients | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 51 | | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height gain month 12 | 9.67 (± 1.84) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height gain after 24 months

| | |
|------------------------|--|
| End point title | Height gain after 24 months ^[8] |
| End point description: | height gain expressed in cm |
| End point type | Primary |
| End point timeframe: | Month 12 to 24 |

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| End point values | All patients | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height gain month 24 | 17.04 (± 2.75) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height gain after 36 months

| | |
|------------------------|--|
| End point title | Height gain after 36 months ^[9] |
| End point description: | height gain expressed in cm |
| End point type | Primary |

End point timeframe:

Month 24 to 36

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height gain month 36 | 24.6 (± 3.21) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height gain SDS

End point title Height gain SDS^[10]

End point description:

Standard Deviation Score (SDS) which is based on the difference between the mean value for normal children of the same gender at that chronological age. SDS values are calculated for height using the following equation: $SDS = (X1 - X2) / SD$ in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

End point type Primary

End point timeframe:

Baseline to month 12

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 51 | | | |
| Units: SDS | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height gain SDS month 12 | -1.48 (± 0.65) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height gain SDS after 24 months

End point title Height gain SDS after 24 months^[11]

End point description:

Standard Deviation Score (SDS) which is based on the difference between the mean value for normal children of the same gender at that chronological age. SDS values are calculated for height using the following equation: $SDS = X1 - X2 / SD$ in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

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

End point timeframe:

Month 12 to 24

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| End point values | All patients | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: SDS | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height gain SDS month 24 | -0.97 (± 0.61) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height gain SDS after 36 months

| | |
|-----------------|---|
| End point title | Height gain SDS after 36 months ^[12] |
|-----------------|---|

End point description:

Standard Deviation Score (SDS) which is based on the difference between the mean value for normal children of the same gender at that chronological age. SDS values are calculated for height using the following equation: $SDS = X1 - X2 / SD$ in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

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

End point timeframe:

Month 24 to 36

Notes:

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

Justification: The whole study was performed only with descriptive analysis.

| End point values | All patients | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Height gain SDS month 36 | -0.71 (± 0.71) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: IGF-1 baseline to month 12

End point title IGF-1 baseline to month 12

End point description:

Increases in IGF-1 levels were calculated every six months. Changes in IGF-1 levels were evaluated for each individual patient and for all subjects.

End point type Secondary

End point timeframe:

Baseline to month 12

| End point values | All patients | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 51 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 64.88 (\pm 54.18) | | | |
| Month 6 | 172.4 (\pm 127) | | | |
| Month 12 | 193.5 (\pm 103.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: IGF-1 month 12 to month 24

End point title IGF-1 month 12 to month 24

End point description:

Increases in IGF-1 levels were calculated every six months. Changes in IGF-1 levels were evaluated for each individual patient and for all subjects.

End point type Secondary

End point timeframe:

Month 12 to 24

| End point values | All patients | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 18 | 208.5 (\pm 79.12) | | | |
| Month 24 | 241.2 (\pm 113) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: IGF-1 month 24 to month 36

| | |
|-----------------|----------------------------|
| End point title | IGF-1 month 24 to month 36 |
|-----------------|----------------------------|

End point description:

Increases in IGF-1 levels were calculated every six months. Changes in IGF-1 levels were evaluated for each individual patient and for all subjects.

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

End point timeframe:

Month 24 to 36

| End point values | All patients | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 36 | 234.5 (± 169.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: IGF-1 SDS baseline to month 12

| | |
|-----------------|--------------------------------|
| End point title | IGF-1 SDS baseline to month 12 |
|-----------------|--------------------------------|

End point description:

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

End point timeframe:

Baseline to month 12

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 51 | | | |
| Units: SDS | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | -1.28 (± 1.26) | | | |
| Month 6 | 0.58 (± 1.77) | | | |
| Month 12 | 0.6 (± 1.48) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: IGF-1 SDS month 12 to month 24

| | |
|------------------------|--------------------------------|
| End point title | IGF-1 SDS month 12 to month 24 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Month 12 to 24 | |

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: SDS | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 18 | 0.91 (± 1.5) | | | |
| Month 24 | 0.6 (± 1.55) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: IGF-1 SDS month 36

| | |
|------------------------|--------------------|
| End point title | IGF-1 SDS month 36 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Month 24 to 36 | |

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: SDS | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 36 | 0.44 (\pm 2.01) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Antibodies against GH - Baseline and Month 12

| | |
|--|---|
| End point title | Antibodies against GH - Baseline and Month 12 |
| End point description: Immunological safety was assessed by assaying for antibodies against GH at a central laboratory. This endpoint was analysed even for patients that dropped out of the study. | |
| End point type | Secondary |
| End point timeframe: 24 Months - assessments where done at baseline, at month 12 and at month 24 | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: Negative / positive | | | | |
| Negative - Baseline | 44 | | | |
| Missing - Baseline | 6 | | | |
| Negative - Month 12 | 42 | | | |
| Missing - Month 12 | 8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Antibodies against GH - Month 24

| | |
|--|----------------------------------|
| End point title | Antibodies against GH - Month 24 |
| End point description: Immunological safety was assessed by assaying for antibodies against GH at a central laboratory. This endpoint was analysed even for patients that dropped out of the study. | |
| End point type | Secondary |

End point timeframe:

24 Months - assessments where done at baseline, at month 12 and at month 24

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | All patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: Negative / Positive | | | | |
| Negative - Month 24 | 25 | | | |
| Missing - Month 24 | 16 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

51 subjects were exposed to the treatment for 12 months, 43 for 18 months, 41 for 24 months and 24 for 36 months, representing about 1400 subject*months

Adverse event reporting additional description:

The following assessments were made at each Visit:

- Local tolerance at the injection site.
- Systemic tolerance through the recording of Adverse Events and concomitant treatments

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events | All patients | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Surgical and medical procedures | | | |
| Appendectomy | Additional description: Appendectomy was performed on 7 May and his hospital stay lasted from 7 - 14 May 2005. During this time, the treatment was interrupted. The Investigator judged the relationship between the event and the Study Treatment as Improbable. | | |
| subjects affected / exposed | 1 / 51 (1.96%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | Additional description: Constipation was diagnosed; he was given an enema and put on Fortax and Spasfon. He completely recovered and was discharged on 17 March 2006. The Investigator judged that no related to study treatment | | |
| subjects affected / exposed | 1 / 51 (1.96%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | All patients | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 51 (82.35%) | | |
| Investigations | | | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | | |
| occurrences (all) | 6 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 51 (19.61%) | | |
| occurrences (all) | 10 | | |
| Gastrointestinal disorders | | | |
| Pharyngitis | | | |
| subjects affected / exposed | 8 / 51 (15.69%) | | |
| occurrences (all) | 8 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinitis | | | |
| subjects affected / exposed | 9 / 51 (17.65%) | | |
| occurrences (all) | 9 | | |
| Cough | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | | |
| occurrences (all) | 6 | | |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 9 / 51 (17.65%) | | |
| occurrences (all) | 9 | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | | |
| occurrences (all) | 6 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 18 May 2004 | Methodological change: increased dose for non-responders in the second year of treatment; change to the Information Sheet; and updating of the list of Investigating Centres |
| 14 December 2004 | Methodological change: change in the central laboratory for anti-GH antibody assays; change in the volumes of blood to be drawn; change of the injector-pen and to the related Questionnaire; date of the preliminary statistical analysis put back (from 30 April 2005 to a later, as yet unfixed date, due to the low inclusion rate); change to the Information Sheet; updating of the list of Investigating Centres; and modification of the Sponsor's legal status. |
| 10 January 2006 | Extension of the inclusion period by one year, through 31 December 2006; changes in the section on SAEs; updating of the Investigator's Brochure (N° 11 of 25 May 2005); and updating of the list of Investigating Centres |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported