



Clinical trial results:

A randomised, open-label, parallel-group, multi-centre trial comparing the efficacy and safety of 12 months treatment with one daily dose of ZOMACTON® to one daily dose of GENOTROPIN® in the treatment of children with idiopathic growth hormone deficiency

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2008-004849-28 |
| Trial protocol | HU |
| Global end of trial date | 25 June 2012 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 01 March 2016 |
| First version publication date | 26 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | FE 999905 CS07 |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Ferring Pharmaceuticals A/S |
| Sponsor organisation address | Kay Fiskers Plads 11, Copenhagen S , Denmark, 2300 |
| Public contact | Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com |
| Scientific contact | Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.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 | 04 July 2012 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 June 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that one daily dose of ZOMACTON (10 mg/mL) is equivalent to one daily dose of GENOTROPIN (12 mg/mL) in terms of growth measured as height velocity based on 12 months of treatment.

Protection of trial subjects:

The target trial population was children aged 3-11 years old, who was unable to provide legally binding consent. Therefore, informed consent had to be sought from the parent(s)/legal representatives on the child's behalf prior to enrolling the child in the trial.

Oral information was given to the children and the parent(s)/legal representatives by an experienced investigator, or adequately trained delegate site staff. The information was also provided in writing. The process of the assent from each child was carried out slowly with an age-appropriate language. The assent process was conducted with sufficient time and at the same time as the consent was obtained from the parent(s)/legal representatives, so that the informed consent reflected the presumed will of the child. Besides the oral information given to the child, information sheet and assent form were provided in an age-appropriate language with wording that corresponded to the child's psychological and intellectual maturity. Adequate time was given to the parent(s)/legal representative to discuss with their child with or without the presence of the Investigator, if required. The child's assent was not sufficient to allow participation in research unless supplemented by informed consent of the parent(s)/legal representatives.

The Investigator obtained freely given, written consent from each child's parent(s)/legal representatives as well as a signed or indicated assent from each child after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial relevant to the decision of the child and parent(s)/ legal representatives' decision to participate.

Background therapy: -

Evidence for comparator:

Growth hormone (GH) is essential for normal growth in children and acts by increasing growth, both via production of insulin-like growth factor (IGF), especially IGF-1, and via direct action on the growth plates. Lack of growth hormone in children leads to impairment of growth and eventually short stature. ZOMACTON is currently approved for treatment of children with growth hormone deficiency and for long-term treatment of growth retardation due to Turner's syndrome (gonadal dysgenesis) confirmed by chromosomal analysis. Other indications for other somatropin-products (e.g., GENOTROPIN) include children born small for gestational age, Prader-Willi's syndrome, patients with chronic renal insufficiency, and adults with growth hormone deficiency with adult or childhood onset. Biosimilarity would allow for expansion of the approved indications for ZOMACTON to include those approved for GENOTROPIN.

| | |
|---|------------------|
| Actual start date of recruitment | 22 November 2009 |
| 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 | India: 24 |
| Country: Number of subjects enrolled | Israel: 30 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Romania: 11 |
| Country: Number of subjects enrolled | Ukraine: 41 |
| Country: Number of subjects enrolled | Russian Federation: 35 |
| Country: Number of subjects enrolled | Poland: 13 |
| Country: Number of subjects enrolled | Hungary: 11 |
| Worldwide total number of subjects | 165 |
| EEA total number of subjects | 35 |

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) | 165 |
| 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 259 subjects were screened in the trial of which 165 subjects were randomised: 82 in the ZOMACTON treatment group and 83 in the GENOTROPIN treatment group.

Pre-assignment

Screening details:

Trial was initiated with a pre-screening period during which time a confirmative standard GH stimulation test had to be performed. It took place up to 3 months (or 5 months in Israel) prior to the actual screening period. Pre-screening period was followed by a screening period which could be up to 21 days prior to actual 12-month treatment period.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Visit 2 (Day 0) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

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

Arm description:

Zomacton 10 mg/mL: It was administered with ZomaJet® Vision X (subcutaneous transjection).

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

Dosage and administration details:

Subjects randomised to ZOMACTON treatment received a daily dose of 0.03 mg/kg/day ZOMACTON (10 mg/mL) for 12 months. ZOMACTON was administered as a subcutaneous transjection using ZomaJet®Vision X.

| | |
|------------------|------------|
| Arm title | Genotropin |
|------------------|------------|

Arm description:

Genotropin 12 mg/mL: It was administered with Genotropin Pen®12 (subcutaneous injection)

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

Dosage and administration details:

Subjects randomised to GENOTROPIN treatment received a daily dose of 0.03 mg/kg/day GENOTROPIN (12 mg/mL) for 12 months. GENOTROPIN was administered as a subcutaneous injection using Genotropin Pen®12.

| Number of subjects in period 1 | Zomacton | Genotropin |
|--------------------------------|----------|------------|
| Started | 82 | 83 |
| Completed | 82 | 83 |

Period 2

| | |
|------------------------------|-------------------------------------|
| Period 2 title | Treatment period (Day 0 - 12 Month) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|--|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Zomacton |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Zomacton |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects randomised to ZOMACTON treatment received a daily dose of 0.03 mg/kg/day ZOMACTON (10 mg/mL) for 12 months. ZOMACTON was administered as a subcutaneous transjection using ZomaJet®Vision X.

| | |
|--|---|
| Arm title | Genotropin |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Genotropin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects randomised to GENOTROPIN treatment received a daily dose of 0.03 mg/kg/day GENOTROPIN (12 mg/mL) for 12 months. GENOTROPIN was administered as a subcutaneous injection using Genotropin Pen®12.

| Number of subjects in period 2 | Zomacton | Genotropin |
|---------------------------------------|----------|------------|
| Started | 82 | 83 |
| Completed | 79 | 82 |
| Not completed | 3 | 1 |
| Consent withdrawn by subject | 1 | - |
| Pre-treatment adverse event | 1 | - |
| Other | - | 1 |
| Lack of efficacy | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|------------|
| Reporting group title | Zomacton |
| Reporting group description: | |
| Zomacton 10 mg/mL: It was administered with ZomaJet® Vision X (subcutaneous transjection). | |
| Reporting group title | Genotropin |
| Reporting group description: | |
| Genotropin 12 mg/mL: It was administered with Genotropin Pen®12 (subcutaneous injection) | |

| Reporting group values | Zomacton | Genotropin | Total |
|--|----------|------------|-------|
| Number of subjects | 82 | 83 | 165 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 82 | 83 | 165 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| All the subjects were paediatric. | | | |
| Units: years | | | |
| arithmetic mean | 7.09 | 7.27 | |
| standard deviation | ± 2.29 | ± 2.2 | - |
| Gender categorical | | | |
| At baseline (at Visit 0) | | | |
| Units: Subjects | | | |
| Female | 27 | 28 | 55 |
| Male | 55 | 55 | 110 |
| Race | | | |
| At baseline (at Visit 0) | | | |
| Units: Subjects | | | |
| Asian | 12 | 13 | 25 |
| Black or African American | 1 | 0 | 1 |
| White | 69 | 70 | 139 |
| Bone age | | | |
| At baseline (at Visit 0) | | | |
| Units: Years | | | |
| arithmetic mean | 4.29 | 4.68 | |
| standard deviation | ± 2.21 | ± 2.09 | - |
| Baseline height | | | |
| At baseline (at Visit 0) | | | |
| Units: cm | | | |

| | | | |
|--------------------------------|--------|--------|---|
| arithmetic mean | 104 | 106 | |
| standard deviation | ± 12.8 | ± 11.7 | - |
| Peak GH stimulation test | | | |
| At baseline (at Visit 0) | | | |
| Units: µg/L | | | |
| arithmetic mean | 3.25 | 2.95 | |
| standard deviation | ± 2.65 | ± 2.31 | - |
| Baseline Body Mass Index (BMI) | | | |
| Units: kg/m/m | | | |
| arithmetic mean | 16 | 16.3 | |
| standard deviation | ± 2.27 | ± 2.43 | - |

Subject analysis sets

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full analysis Set (FAS) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The FAS comprised data from all randomised and treated subjects. If a subject received incorrect treatment (i.e., the actual treatment was not as randomised), he or she was included in the group reflecting the actual treatment received.

| | |
|----------------------------|--------------------------------|
| Subject analysis set title | Per Protocol (PP) Analysis Set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Subjects in the FAS analysis set were excluded from the PP analysis set if they met any of the pre-specified criteria of protocol deviation or otherwise excluded due to any serious unforeseen violations deemed to invalidate the data and affect the conclusions of the trial.

| | |
|----------------------------|---------------------|
| Subject analysis set title | Safety Analysis set |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The definition of the safety analysis set was identical to the FAS.

| Reporting group values | Full analysis Set (FAS) | Per Protocol (PP) Analysis Set | Safety Analysis set |
|--|-------------------------|--------------------------------|---------------------|
| Number of subjects | 165 | 153 | 165 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 165 | 153 | 165 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| All the subjects were paediatric. | | | |
| Units: years | | | |
| arithmetic mean | 7.18 | 7.15 | 7.18 |
| standard deviation | ± 2.24 | ± 2.26 | ± 2.24 |

| | | | |
|--------------------------------|--------|--------|--------|
| Gender categorical | | | |
| At baseline (at Visit 0) | | | |
| Units: Subjects | | | |
| Female | 55 | 51 | 55 |
| Male | 110 | 102 | 110 |
| Race | | | |
| At baseline (at Visit 0) | | | |
| Units: Subjects | | | |
| Asian | 25 | 22 | 25 |
| Black or African American | 1 | 1 | 1 |
| White | 139 | 130 | 139 |
| Bone age | | | |
| At baseline (at Visit 0) | | | |
| Units: Years | | | |
| arithmetic mean | 4.48 | 4.44 | 4.48 |
| standard deviation | ± 2.16 | ± 2.17 | ± 2.16 |
| Baseline height | | | |
| At baseline (at Visit 0) | | | |
| Units: cm | | | |
| arithmetic mean | 105 | 105 | 105 |
| standard deviation | ± 12.3 | ± 12.4 | ± 12.3 |
| Peak GH stimulation test | | | |
| At baseline (at Visit 0) | | | |
| Units: µg/L | | | |
| arithmetic mean | 3.1 | 3.07 | 3.1 |
| standard deviation | ± 2.48 | ± 2.47 | ± 2.48 |
| Baseline Body Mass Index (BMI) | | | |
| Units: kg/m/m | | | |
| arithmetic mean | 16.1 | 16.2 | 16.1 |
| standard deviation | ± 2.35 | ± 2.35 | ± 2.35 |

End points

End points reporting groups

| | |
|--|--------------------------------|
| Reporting group title | Zomacton |
| Reporting group description: Zomacton 10 mg/mL: It was administered with ZomaJet® Vision X (subcutaneous transjection). | |
| Reporting group title | Genotropin |
| Reporting group description: Genotropin 12 mg/mL: It was administered with Genotropin Pen®12 (subcutaneous injection) | |
| Reporting group title | Zomacton |
| Reporting group description: - | |
| Reporting group title | Genotropin |
| Reporting group description: - | |
| Subject analysis set title | Full analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The FAS comprised data from all randomised and treated subjects. If a subject received incorrect treatment (i.e., the actual treatment was not as randomised), he or she was included in the group reflecting the actual treatment received. | |
| Subject analysis set title | Per Protocol (PP) Analysis Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Subjects in the FAS analysis set were excluded from the PP analysis set if they met any of the pre-specified criteria of protocol deviation or otherwise excluded due to any serious unforeseen violations deemed to invalidate the data and affect the conclusions of the trial. | |
| Subject analysis set title | Safety Analysis set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The definition of the safety analysis set was identical to the FAS. | |

Primary: Height velocity (HV) - Full analysis set

| | |
|---|--|
| End point title | Height velocity (HV) - Full analysis set |
| End point description: The HV was defined as: (height at visit – height at baseline) / actual length of time between the two measurements. | |
| End point type | Primary |
| End point timeframe: 12 months treatment | |

| End point values | Zomacton | Genotropin | Full analysis Set (FAS) | |
|--------------------------------------|-----------------|-----------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 80 | 82 | 162 ^[1] | |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | 10.7 (± 3.07) | 10.9 (± 3.42) | 10.8 (± 3.25) | |

Notes:

[1] - Total no. of subjects at month 12 ' End of trial' Visit.

| | |
|-----------------------------------|--|
| Attachments (see zip file) | HV Last Observation Carried Forward (LOCF)/Height Velocity |
|-----------------------------------|--|

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | ANCOVA of Height velocity at Month 12 (LOCF) - FAS |
|-----------------------------------|--|

Statistical analysis description:

Height velocity was analysed using an Analysis of Covariance (ANCOVA) model with baseline Chronological Age (CA), baseline HV, and log peak GH level after stimulation, as covariates and country, sex and treatment as factors.

Equivalence was declared since the 95% confidence interval (CI) for the difference in HV was with [-2.0 ; 2.0] for both FAS and PP.

| | |
|---|--------------------------------|
| Comparison groups | Zomacton v Genotropin |
| Number of subjects included in analysis | 162 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 1.1 |

Primary: Height velocity - PP analysis set

| | |
|-----------------|-----------------------------------|
| End point title | Height velocity - PP analysis set |
|-----------------|-----------------------------------|

End point description:

The HV was defined as: (height at visit – height at baseline) / actual length of time between the two measurements.

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

End point timeframe:

12 months treatment

| End point values | Zomacton | Genotropin | Per Protocol (PP) Analysis Set | |
|--------------------------------------|-----------------|-----------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 74 | 74 | 148 ^[2] | |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | 10.9 (± 3.07) | 11.1 (± 3.23) | 11 (± 3.15) | |

Notes:

[2] - Total no. of subjects at month 12 ' End of trial' Visit.

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | ANCOVA of Height velocity at Month 12 (LOCF) - PP |
|-----------------------------------|---|

Statistical analysis description:

Height velocity was analysed using an ANCOVA model with baseline CA, baseline HV, and log peak GH

level after stimulation, as covariates and country, sex and treatment as factors.

Equivalence was declared since the 95% CI for the difference in HV was with [-2.0 ; 2.0] for both FAS and PP.

| | |
|---|--------------------------------|
| Comparison groups | Zomacton v Genotropin |
| Number of subjects included in analysis | 148 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 1.1 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were monitored continuously throughout the study from the time of obtaining informed consent until the end of trial.

Adverse event reporting additional description:

At each visit, AEs were elicited using a standard non-leading question. Adverse events could also be captured by symptoms spontaneously reported from the subject or as results of clinically significant changes and abnormalities observed by the Investigator. In addition, AEs were recorded in a booklet between the visits.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 12.1 |

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Zomacton |
|-----------------------|----------|

Reporting group description:

Zomacton 10 mg/mL: It was administered with ZomaJet® Vision X (subcutaneous transjection).

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

Reporting group description:

Genotropin 12 mg/mL: It was administered with Genotropin Pen®12 (subcutaneous injection)

| Serious adverse events | Zomacton | Genotropin | |
|--|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 0 / 83 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| abnormal behaviour | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Zomacton | Genotropin | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 82 (43.90%) | 31 / 83 (37.35%) | |
| Investigations | | | |
| Insulin-like growth factor decreased | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 6 / 83 (7.23%) | |
| occurrences (all) | 6 | 9 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 6 / 82 (7.32%) | 3 / 83 (3.61%) | |
| occurrences (all) | 6 | 7 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 5 / 83 (6.02%) | |
| occurrences (all) | 3 | 6 | |
| General disorders and administration site conditions | | | |

| | | | |
|--|-----------------------|----------------------|--|
| Injection site haematoma subjects affected / exposed occurrences (all) | 9 / 82 (10.98%) 10 | 4 / 83 (4.82%) 5 | |
| Pyrexia subjects affected / exposed occurrences (all) | 6 / 82 (7.32%) 10 | 7 / 83 (8.43%) 9 | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 7 / 82 (8.54%) 8 | 7 / 83 (8.43%) 11 | |
| Pharyngitis subjects affected / exposed occurrences (all) | 7 / 82 (8.54%) 9 | 1 / 83 (1.20%) 1 | |
| Viral infection subjects affected / exposed occurrences (all) | 5 / 82 (6.10%) 5 | 3 / 83 (3.61%) 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 22 December 2009 | <p>The original protocol required an X-ray for determination of bone age (BA) at baseline (performed at the screening). However, at some sites, an X-ray had already been taken prior to the pre-screening visit. Therefore, to avoid repeated X-rays, the period for performing this X-ray was extended. An X-ray taken within 3 months prior to visit 2 was acceptable.</p> <p>"The difference between CA-BA ≥ 1" was an inclusion criterion in original protocol whereas "BA above 9 years in girls and above 10 years in boys" was an exclusion criterion. This was to reassure that the subject was at pre-pubertal stage upon enrolment of the trial and able to complete the 12-month treatment period prior to entering the puberty. However, the restriction of "CA-BA ≥ 1" was not relevant for younger children. Therefore, the inclusion criterion was changed to "BA/CA ≤ 0.9".</p> <p>The baseline GH level for inclusion was changed from "9 ng/mL" to "10 ng/mL" as this was the cut-point value for initiation of GH treatment.</p> <p>Any use of corticoid steroids and medications that could interfere with GH treatment was prohibited in the original protocol. However, some children may suffer from adrenocorticotrophic hormone deficiency and for these children glucocorticosteroid treatments are mandatory as physiological replacement. Hence, glucocorticosteroid treatment was allowed as long as it was at a stable dose level.</p> <p>As per exclusion criteria in the original protocol, children with any diagnosed or suspected severe chronic disease or clinical signs of dysmorphic features, malformations, or mental retardation were not allowed to be included in the trial. However, a child with minor dysmorphic features or malformation in stable condition could be enrolled into the trial as long as it doesn't place the child at excessive risk by participating in the trial, and therefore, the exclusion criteria were changed.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported