



Clinical trial results:

Recombinant Human Insulin-Like Growth Factor-1 (rhIGF-1) Treatment of Short Stature Associated With Primary IGF-1 Deficiency: A Multicenter, Open-Label, Concentration-Controlled Trial

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2019-001095-11 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 14 January 2009 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 22 September 2019 |
| First version publication date | 22 September 2019 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | MS308 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00125190 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Ipsen Pharma |
| Sponsor organisation address | 65 Quai Georges Gorse, Boulogne Billancourt, France, 92100 |
| Public contact | Medical Director, Ipsen Pharma, clinical.trials@ipsen.com |
| Scientific contact | Medical Director, Ipsen Pharma, clinical.trials@ipsen.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 | 14 January 2009 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 January 2009 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to assess the effects of once daily (QD) dosing with rhIGF-1 in increasing height velocity in prepubertal subjects with growth failure associated with primary insulin-like growth factor deficiency (IGFD).

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice, as set out in the Code of Federal Regulations (CFR) 21 CFR paragraphs 50 and 312.60. International Conference on Harmonisation E6, (1996), the ethical principles that have their origins in the Declaration of Helsinki (revised Edinburgh, 2000), and applicable national and local regulatory requirements. In this pediatric trial, the Investigator or his/her delegate obtained written informed consent signed by each subject's parent or a duly authorized representative prior to conducting any protocol-related activity.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 12 January 2005 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 45 |
| Worldwide total number of subjects | 45 |
| EEA total number of subjects | 0 |

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) | 36 |
| Adolescents (12-17 years) | 9 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

First subject screened: 12 January 2005. Last subject completed: 14 January 2009. 12 investigators screened subjects, 1 did not enroll any subjects. 89 subjects were screened, 41 were ineligible, 3 declined treatment and 45 were treated and analyzed.

Pre-assignment

Screening details:

Screening consisted of two-staged clinic visits for up to 6 weeks, and included the following evaluations: medical history, complete physical examination, measurements of serum IGF-1 and IGF-1 binding proteins (IGFBP-1, IGFBP-2 and IGFBP-3), growth hormone (GH) binding protein, acid-labile subunit (ALS), GH stimulation test.

Period 1

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

Arms

| | |
|-----------|------------|
| Arm title | rhIGF-1 QD |
|-----------|------------|

Arm description:

During the treatment phase (Day 1 to Week 86), subjects received subcutaneous (SC) injections of rhIGF-1 at an initial dose of 60 microgram per kilogram (mcg/kg) QD starting on Day 1 (Visit 3). From Week 2 (Visit 4) subsequent dose adjustments were made in order to achieve the target serum IGF-1 concentration for the subject's age and sex.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | rhIGF-1 |
| Investigational medicinal product code | |
| Other name | Increlex®, Mecasermin |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

An initial dose of 60 mcg/kg QD with subsequent dose adjustments made in order to achieve the target serum IGF-1 concentration for the subject's age and sex. The maximum dose in any circumstance was 240 mcg/kg/day. The injection sites were rotated to minimize potential injection site reactions.

| Number of subjects in period 1 | rhIGF-1 QD |
|--------------------------------|------------|
| Started | 45 |
| Completed 34 weeks of study | 43 |
| Completed | 30 |
| Not completed | 15 |
| Adverse event, non-fatal | 1 |
| Subject/Parent Decision | 7 |
| Non-compliance | 2 |
| Unspecified | 1 |
| Lost to follow-up | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | rhIGF-1 QD |
|-----------------------|------------|

Reporting group description:

During the treatment phase (Day 1 to Week 86), subjects received subcutaneous (SC) injections of rhIGF-1 at an initial dose of 60 microgram per kilogram (mcg/kg) QD starting on Day 1 (Visit 3). From Week 2 (Visit 4) subsequent dose adjustments were made in order to achieve the target serum IGF-1 concentration for the subject's age and sex.

| Reporting group values | rhIGF-1 QD | Total | |
|--|------------|-------|--|
| Number of subjects | 45 | 45 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 36 | 36 | |
| Adolescents (12-17 years) | 9 | 9 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 8.7 | | |
| standard deviation | ± 2.8 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | 7 | |
| Male | 38 | 38 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Black | 1 | 1 | |
| Hispanic | 12 | 12 | |
| White | 31 | 31 | |
| Other | 1 | 1 | |
| Body Mass Index Standard Deviation (SD) Score | | | |
| Units: SDs | | | |
| arithmetic mean | -0.4 | | |
| standard deviation | ± 0.7 | - | |
| Bone Age Imputed | | | |
| Units: years | | | |
| arithmetic mean | 7.2 | | |
| standard deviation | ± 2.6 | - | |
| Height for Age SD Score | | | |
| Units: SDs | | | |
| arithmetic mean | -2.7 | | |

| | | | |
|--------------------------------|-----------|---|--|
| standard deviation | ± 0.6 | - | |
| IGFBP-3 SD Score | | | |
| Units: SDs | | | |
| arithmetic mean | -0.7 | | |
| standard deviation | ± 1.0 | - | |
| IGF-1 SD Score | | | |
| Units: SDs | | | |
| arithmetic mean | -2.6 | | |
| standard deviation | ± 0.5 | - | |
| Maximum Stimulated GH | | | |
| Units: nanogram per milliliter | | | |
| arithmetic mean | 20.5 | | |
| standard deviation | ± 9.9 | - | |
| Weight for Age SD Score | | | |
| Units: SDs | | | |
| arithmetic mean | -2.3 | | |
| standard deviation | ± 0.7 | - | |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | rhIGF-1 QD |
| Reporting group description: | |
| During the treatment phase (Day 1 to Week 86), subjects received subcutaneous (SC) injections of rhIGF-1 at an initial dose of 60 microgram per kilogram (mcg/kg) QD starting on Day 1 (Visit 3). From Week 2 (Visit 4) subsequent dose adjustments were made in order to achieve the target serum IGF-1 concentration for the subject's age and sex. | |

Primary: Height Velocity Over the Study Period Pretreatment (Week 0) - 34 Weeks: Intent to Treat (ITT) Population

| | |
|-----------------|---|
| End point title | Height Velocity Over the Study Period Pretreatment (Week 0) - 34 Weeks: Intent to Treat (ITT) Population ^[1] |
|-----------------|---|

End point description:

Height was measured standing without shoes as the average of three measurements by the same observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject was repositioned between each measurement. The ITT principle was used for the primary analysis, with imputation of missing height velocity and missing height SD score. Height velocity during an interval of time is defined as the change in height during the time interval divided by the duration of the time interval.

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

End point timeframe:

Pretreatment to Week 34

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: Descriptive statistical analysis was performed for the outcome measure.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: centimeter per year (cm/yr) | | | | |
| arithmetic mean (standard deviation) | 7.0 (± 1.5) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Height Velocity Over the Study Period 34 - 86 Weeks: ITT Population

| | |
|-----------------|--|
| End point title | Height Velocity Over the Study Period 34 - 86 Weeks: ITT Population ^[2] |
|-----------------|--|

End point description:

Height was measured standing without shoes as the average of three measurements by the same observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject was repositioned between each measurement. The ITT principle was used for the primary analysis, with imputation of missing height velocity and missing height SD score. Height velocity during an interval of time is defined as the change in height during the time interval divided by the duration of the time interval. Only subjects in the ITT population who continued past Week 34 were included in the analysis.

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

End point timeframe:

Weeks 34 to 86

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: Descriptive statistical analysis was performed for the outcome measure.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: cm/yr | | | | |
| arithmetic mean (standard deviation) | 6.7 (± 1.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Height SD Score From Pretreatment to Week 34: ITT Population

| | |
|-----------------|---|
| End point title | Changes in Height SD Score From Pretreatment to Week 34: ITT Population |
|-----------------|---|

End point description:

Height was measured standing without shoes as the average of three measurements by the same observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject was repositioned between each measurement. The SD score is calculated as the subject value minus the mean divided by the standard deviation. The mean and the standard deviation vary depending on the age and sex of the child. The ITT principle was used for missing height SD score.

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

End point timeframe:

Pretreatment and Week 34

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: SDs | | | | |
| arithmetic mean (standard deviation) | 0.21 (± 0.20) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Height SD Score From Pretreatment to Week 86: ITT Population

| | |
|-----------------|---|
| End point title | Changes in Height SD Score From Pretreatment to Week 86: ITT Population |
|-----------------|---|

End point description:

Height was measured standing without shoes as the average of three measurements by the same observer using identical technique with a Harpenden or other wall mounted stadiometer. Subjects were repositioned between each measurement. The SD score is calculated as the patient value minus the mean divided by the standard deviation. The mean and the standard deviation vary depending on the age and sex of the child. The ITT principle was used for missing height SD score. Only subjects in the ITT population who continued past Week 86 were included in the analysis.

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

End point timeframe:

Pretreatment and Week 86

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: SDs | | | | |
| arithmetic mean (standard deviation) | 0.45 (\pm 0.39) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Bone Age From Pretreatment to Week 86 Minus Change in Chronological Age: ITT Population

| | |
|-----------------|---|
| End point title | Change in Bone Age From Pretreatment to Week 86 Minus Change in Chronological Age: ITT Population |
|-----------------|---|

End point description:

Plain X-rays of the left hand and wrist were exposed for bone age appraisal. The films were sent to a central facility for standardized evaluation. Subjects who had both pretreatment and Week 86 measurements were included in the analysis.

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

End point timeframe:

Pretreatment to Week 86

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: years | | | | |
| arithmetic mean (standard deviation) | 0.2 (\pm 0.68) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Changes in Serum Concentration of IGFBP-1 From Pretreatment to Week 86

| | |
|--|--|
| End point title | Percent Changes in Serum Concentration of IGFBP-1 From Pretreatment to Week 86 |
| End point description: Growth factor panels for measuring IGFBP-1 were evaluated from screening and at each study visit up to Week 86. Inter-quartile range (Q1-Q3) is 10th to 90th percentile. | |
| End point type | Secondary |
| End point timeframe: Pretreatment and Week 86 | |

| | | | | |
|---------------------------------------|--------------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | -89.6 (-96 to -13) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Changes in Serum Concentration of IGFBP-2 From Pretreatment to Week 86

| | |
|---|--|
| End point title | Percent Changes in Serum Concentration of IGFBP-2 From Pretreatment to Week 86 |
| End point description: Growth factor panels for measuring IGFBP-2 were evaluated from screening and at each study visit up to Week 86. Subjects who had both pretreatment and Week 86 measurements were included in the analysis. Inter-quartile range (Q1-Q3) is 10th to 90th percentile. | |
| End point type | Secondary |
| End point timeframe: Pretreatment and Week 86 | |

| | | | | |
|---------------------------------------|-------------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | 37.9 (-25 to 227) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Changes in Serum Concentration of IGFBP-3 From Pretreatment to Week 86

| | |
|---|--|
| End point title | Percent Changes in Serum Concentration of IGFBP-3 From Pretreatment to Week 86 |
| End point description: Growth factor panels for measuring IGFBP-3 were evaluated from screening and at each study visit up to Week 86. Subjects who had both pretreatment and Week 86 measurements were included in the analysis. Inter-quartile range (Q1-Q3) is 10th to 90th percentile. | |
| End point type | Secondary |
| End point timeframe: Pretreatment and Week 86 | |

| | | | | |
|---------------------------------------|-----------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | 0 (-27 to 48) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Changes in Serum Concentration of ALS From Pretreatment to Week 86

| | |
|---|--|
| End point title | Percent Changes in Serum Concentration of ALS From Pretreatment to Week 86 |
| End point description: Growth factor panels for measuring ALS were evaluated from screening and at each study visit up to Week 86. Subjects who had both pretreatment and Week 86 measurements were included in the analysis. Inter-quartile range (Q1-Q3) is 10th to 90th percentile. | |
| End point type | Secondary |
| End point timeframe: Pretreatment and Week 86 | |

| | | | | |
|---------------------------------------|------------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | -7.7 (-36 to 42) | | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Increase in Height Velocity From Pretreatment to Week 34: Completer Population

| | |
|-----------------|--|
| End point title | Increase in Height Velocity From Pretreatment to Week 34: Completer Population |
|-----------------|--|

End point description:

Height was measured standing without shoes as the average of three measurements by the same observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject was repositioned between each measurement. The ITT principle was used for missing height velocity. Height velocity during an interval of time is defined as the change in height during the time interval divided by the duration of the time interval. Only subjects in the ITT population who continued past Week 34 were included in the analysis.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Pretreatment to Week 34

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: cm/yr | | | | |
| arithmetic mean (standard deviation) | 1.3 (\pm 3.56) | | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Increase in Height Velocity From Pretreatment to Week 86: Completer Population

| | |
|-----------------|--|
| End point title | Increase in Height Velocity From Pretreatment to Week 86: Completer Population |
|-----------------|--|

End point description:

Height was measured standing without shoes as the average of three measurements by the same observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject was repositioned between each measurement. The ITT principle was used for missing height velocity. Height velocity during an interval of time is defined as the change in height during the time interval divided by the duration of the time interval. Only subjects in the ITT population who continued past Week 86 were included in the analysis.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Pretreatment to Week 86

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | rhIGF-1 QD | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: cm/yr | | | | |
| arithmetic mean (standard deviation) | 1.3 (\pm 3.58) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected from Day 1 to Week 86 (approximately 21 months).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | rhIGF-1 QD |
|-----------------------|------------|

Reporting group description:

During the treatment phase (Day 1 to Week 86), subjects received SC injections of rhIGF-1 at an initial dose of 60 mcg/kg QD starting on Day 1 (Visit 3). From Week 2 (Visit 4) subsequent dose adjustments were made in order to achieve the target serum IGF-1 concentration for the subject's age and sex.

| Serious adverse events | rhIGF-1 QD | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Congenital, familial and genetic disorders | | | |
| Arnold-Chiari Malformation | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Syringomyelia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| Non-serious adverse events | rhIGF-1 QD | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 41 / 45 (91.11%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 18 / 45 (40.00%) | | |
| occurrences (all) | 32 | | |
| General disorders and administration site conditions | | | |
| Injection Site Bruising | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 5 | | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 45 (31.11%) | | |
| occurrences (all) | 18 | | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 4 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 45 (11.11%) | | |
| occurrences (all) | 6 | | |
| Stomach Discomfort | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | | |
| occurrences (all) | 3 | | |
| Vomiting | | | |
| subjects affected / exposed | 18 / 45 (40.00%) | | |
| occurrences (all) | 21 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 11 / 45 (24.44%) | | |
| occurrences (all) | 13 | | |
| Nasal Congestion | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pharyngolaryngeal Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rhinorrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 45 (13.33%)</p> <p>9</p> <p>4 / 45 (8.89%)</p> <p>5</p> <p>3 / 45 (6.67%)</p> <p>3</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Dermatitis Contact</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 45 (6.67%)</p> <p>3</p> <p>5 / 45 (11.11%)</p> <p>7</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 45 (13.33%)</p> <p>8</p> | | |
| <p>Infections and infestations</p> <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastroenteritis Viral</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Influenza</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Otitis Media</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sinusitis</p> | <p>6 / 45 (13.33%)</p> <p>8</p> <p>3 / 45 (6.67%)</p> <p>4</p> <p>5 / 45 (11.11%)</p> <p>6</p> <p>3 / 45 (6.67%)</p> <p>5</p> <p>5 / 45 (11.11%)</p> <p>7</p> | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 4 | | |
| Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 13 / 45 (28.89%) 24 | | |
| Viral Infection subjects affected / exposed occurrences (all) | 7 / 45 (15.56%) 13 | | |
| Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 14 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 23 November 2004 | The text describing the hypothesis of non-inferiority was rewritten, using standard statistical terms. Text was amended to clarify that GH was a required test at Visit 2 (screening visit) for all subjects, regardless of whether a prior GH stimulation test had been performed. Text was corrected to indicate that both IGF-1 and IGFBP-3 serial sampling were to be performed at Visit 8. The number of subjects required to be screened to achieve the target sample size was revised, based on a lower estimate of the potential drop-out rate. Because GH stimulation tests results are not age-dependent, the restriction that a prior GH stimulation test must have been performed in the past 4 months was removed. Because a 4-month height velocity cannot accurately predict subsequent growth rates, nor is helpful in identifying subjects who can benefit from rhIGF-1 therapy, the 4-month height velocity eligibility criterion was dropped. The phrase, "suspected deletion of the GH gene" was removed from exclusion criterion #1 because it was redundant. The Week 34 visit window was changed to allow for greater flexibility in scheduling. The language regarding statistical case 4 ("non-inferiority test is not significant for either IGF-1 SD score or change in height SD score") was edited for clarity. |
| 20 May 2005 | The twice-daily (BID) arm was removed from study design and all subjects received QD dosing with rhIGF-1. To affect an overall mean 24-hour serum IGF-1 SD score closer to intended average of +1, IGF-1 target concentration at sampling times was changed to 1.4 times concentration corresponding to a mean 24-hour SD score of +1. The word "randomized" was deleted from the study title. The study objective regarding BID dosing was deleted. The study objective regarding QD dosing was changed. The number of subjects treated was changed from 90 to 45, reflecting removal of the BID treatment arm. The chronological age eligibility criterion was expanded, and a bone age eligibility criterion was added. A change to the eligibility of subjects with chronic illness was made to allow consideration of enrollment of subjects with chronic illnesses whose condition or medication did not increase risk to subject or the integrity of study. The rhIGF-1 dosing rules were changed from a computation based on the subject's age at randomization to a computation based on a target IGF-1 concentration that more closely approaches the SD score value of +1. The rhIGF-1 dosing instructions were revised to require that rhIGF-1 be taken in the morning, within 30 minutes of breakfast. The starting dose of rhIGF-1 was changed from 40 mcg/kg to 60 mcg/kg to allow the target serum IGF-1 level to be reached more efficiently and to ensure that physiological replacement levels of IGF-1 are maintained for a longer period of time during the study. Explanatory text was added advising that if the morning rhIGF-1 dose has not been taken on Visit days, the Visit must be rescheduled. This was necessary because without rhIGF-1 administration, IGF-1 levels would be low, leading to an unwarranted rhIGF-1 dose increase. The estimated total number of subjects to be screened at Visit 1 was changed from 205 to 100, and the total estimated number of subjects screened at Visit 2 was changed from 135 to 67. |
| 30 January 2006 | The treatment period was extended by 12 months (to Week 86). Screening rules were changed to allow prior IGF-1 test results to be averaged with Visit 1 screening results in fulfilment of screening criteria. Screening rules were changed to allow Visit 2 and Visit 3 screening tests to be combined, if all eligibility criteria are were met. An additional safety and efficacy analysis point was added at the end of the extension period (at Week 86). Funduscopic examination was added as a safety endpoint. Urine pregnancy test was added for post-menarchal female subjects. Pregnancy was added as a criterion for removal of a subject from the study. Instructions regarding timing of rhIGF-1 dose administration was changed from "within 30 minutes of a meal or snack" to "shortly before or after (+ 20 minutes) a meal or snack". The text regarding FDA approval of rhIGF-1 (Increlex) for the long-term treatment for growth failure in children with severe primary IGFD was updated. |

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| 01 February 2007 | The serum IGF-1 SD score adjustment target was raised from +1 to +2. The maximum permitted QD dose of rhIGF-1 was changed from 160 mcg/kg to 240 mcg/kg. The serum IGF-1 concentration target for each subject was modified at each visit to keep targets commensurate with the subjects' chronological age. |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported