



Clinical trial results:

Long-term phase IV multicenter study on the safety and efficacy of Omnitrope® (rhGH) in short children born Small for Gestational Age (SGA)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2006-002506-58 |
| Trial protocol | HU DE CZ PL BE |
| Global end of trial date | 25 March 2022 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 11 October 2022 |
| First version publication date | 11 October 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CEP00-401 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00537914 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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 | 25 March 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 25 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the long-term effect of growth hormone treatment on the development of diabetes in short children born SGA during treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 06 February 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Poland: 213 |
| Country: Number of subjects enrolled | Georgia: 20 |
| Country: Number of subjects enrolled | Romania: 16 |
| Country: Number of subjects enrolled | Hungary: 11 |
| Country: Number of subjects enrolled | Czechia: 9 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Worldwide total number of subjects | 278 |
| EEA total number of subjects | 258 |

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) | 253 |
| Adolescents (12-17 years) | 25 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study was carried out in 31 centers in 7 countries (Poland, Romania, Hungary, Czech Republic, Germany, Belgium and Georgia).

Pre-assignment

Screening details:

This study was not randomized. All enrolled patients received Omnitrope

Period 1

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

Arms

| | |
|-----------|-----------|
| Arm title | Omnitrope |
|-----------|-----------|

Arm description:

All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Somatropin |
| Investigational medicinal product code | EP2000 |
| Other name | Omnitrope |
| Pharmaceutical forms | Solution for injection, Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.

| Number of subjects in period 1 | Omnitrope |
|--------------------------------|-----------|
| Started | 278 |
| Full analysis set (FAS) | 278 |
| Safety analysis set (SAS) | 277 |
| Completed | 166 |
| Not completed | 112 |
| Adverse event, serious fatal | 1 |
| Treatment failure | 10 |
| Adverse event, non-fatal | 7 |
| patients documented other | 16 |
| Lost to follow-up | 19 |
| Withdrawal of informed consent | 59 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Omnitrope |
|-----------------------|-----------|

Reporting group description:

All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.

| Reporting group values | Omnitrope | Total | |
|--|-----------|-------|--|
| Number of subjects | 278 | 278 | |
| 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) | 253 | 253 | |
| Adolescents (12-17 years) | 25 | 25 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 7.36 | | |
| standard deviation | ± 2.70 | - | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 130 | 130 | |
| Male | 148 | 148 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Caucasian | 276 | 276 | |
| Oriental | 1 | 1 | |
| Mixed ethnic origin (Arabic/Caucasian) | 1 | 1 | |
| Black | 0 | 0 | |

End points

End points reporting groups

| | |
|--|-----------|
| Reporting group title | Omnitrope |
| Reporting group description: All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits. | |

Primary: Number of participants with development of diabetes in short children born SGA during treatment

| | |
|--|--|
| End point title | Number of participants with development of diabetes in short children born SGA during treatment ^[1] |
| End point description: The development of diabetes in short children born SGA during treatment was evaluated based on the carbohydrate metabolism parameters FPG, HbA1c and OGTT (basal and 2-h plasma glucose). Only cases which were confirmed by the investigator were included. | |
| End point type | Primary |
| End point timeframe: throughout the study, approximately 13 years | |
| 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: No statistical analysis were performed for this outcome | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Omnitrope | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 277 | | | |
| Units: Participants | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Height (H) (cm) from baseline

| | |
|--|--|
| End point title | Mean change in Height (H) (cm) from baseline |
| End point description: Mean change in Height from baseline for all patients was reported. | |
| End point type | Secondary |
| End point timeframe: Baseline, 1 year, 2 years, 5 years and 9 years | |

| End point values | Omnitrope | | | |
|---|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 278 | | | |
| Units: cm | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| 1 year | 9.08 (8.89 to 9.27) | | | |
| 2 years | 16.52 (16.22 to 16.82) | | | |
| 5 years | 35.10 (34.48 to 35.72) | | | |
| 9 years | 58.07 (56.83 to 59.30) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Height standard deviation score over time (H SDS) from baseline

| | |
|---|--|
| End point title | Mean change in Height standard deviation score over time (H SDS) from baseline |
| End point description: Mean change in Height standard deviation score over time (H SDS) from baseline was reported. | |
| End point type | Secondary |
| End point timeframe: Baseline, 3 months, 0.5 year, 9 months, 1 year, 1.25 years, 1.5 years, 1.75 years, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 12.5 years | |

| End point values | Omnitrope | | | |
|---|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 278 | | | |
| Units: cm | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| 3 months | 0.30 (0.28 to 0.33) | | | |
| 0.5 year | 0.51 (0.47 to 0.54) | | | |
| 9 months | 0.68 (0.64 to 0.72) | | | |
| 1 year | 0.81 (0.76 to 0.86) | | | |
| 1.25 years | 0.93 (0.87 to 0.98) | | | |
| 1.5 years | 1.04 (0.98 to 1.10) | | | |
| 1.75 years | 1.16 (1.09 to 1.22) | | | |

| | | | | |
|------------|---------------------|--|--|--|
| 2 years | 1.25 (1.18 to 1.31) | | | |
| 3 years | 1.50 (1.42 to 1.58) | | | |
| 4 years | 1.67 (1.57 to 1.77) | | | |
| 5 years | 1.82 (1.70 to 1.94) | | | |
| 6 years | 1.94 (1.81 to 2.07) | | | |
| 7 years | 2.07 (1.92 to 2.22) | | | |
| 8 years | 2.19 (2.03 to 2.35) | | | |
| 9 years | 2.18 (1.99 to 2.37) | | | |
| 10 years | 2.21 (2.00 to 2.43) | | | |
| 11 years | 2.38 (2.13 to 2.63) | | | |
| 12 years | 2.39 (1.81 to 2.97) | | | |
| 12.5 years | 3.01 (1.78 to 4.24) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Height velocity (HV) (cm/year) over time from baseline

| | |
|-----------------|---|
| End point title | Mean change in Height velocity (HV) (cm/year) over time from baseline |
|-----------------|---|

End point description:

Mean change in Height velocity (HV) (cm/year) over time from baseline was reported.

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

End point timeframe:

Baseline, 1 year, 2 years, 5 years and 9 years

| End point values | Omnitrope | | | |
|---|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 278 | | | |
| Units: cm/year | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| 1 year | 4.71 (4.47 to 4.96) | | | |
| 2 years | 3.02 (2.80 to 3.25) | | | |
| 5 years | 1.37 (1.01 to 1.73) | | | |
| 9 years | 0.10 (-0.53 to 0.74) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Height velocity standard deviation score (HV SDS) over time from baseline

| | |
|-----------------|--|
| End point title | Mean change in Height velocity standard deviation score (HV SDS) over time from baseline |
|-----------------|--|

End point description:

Mean change in Height velocity standard deviation score (HV SDS) over time from baseline was reported.

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

End point timeframe:

Baseline, Baseline, 3 months, 0.5 year, 9 months, 1 year, 1.25 years, 1.5 years, 1.75 years, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 12.5 years

| End point values | Omnitrope | | | |
|---|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 278 | | | |
| Units: cm/year | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| 3 months | 8.41 (7.76 to 9.07) | | | |
| 0.5 year | 7.27 (6.83 to 7.71) | | | |
| 9 months | 6.69 (6.31 to 7.06) | | | |
| 1 year | 6.26 (5.92 to 6.59) | | | |
| 1.25 years | 5.29 (4.99 to 5.60) | | | |
| 1.5 years | 4.85 (4.55 to 5.15) | | | |
| 1.75 years | 4.59 (4.28 to 4.91) | | | |
| 2 years | 4.35 (4.02 to 4.68) | | | |
| 3 years | 3.62 (3.23 to 4.00) | | | |
| 4 years | 3.08 (2.68 to 3.47) | | | |
| 5 years | 2.99 (2.50 to 3.49) | | | |
| 6 years | 2.63 (2.14 to 3.13) | | | |
| 7 years | 2.43 (1.95 to 2.92) | | | |

| | | | | |
|------------|----------------------|--|--|--|
| 8 years | 1.37 (0.75 to 1.98) | | | |
| 9 years | 0.85 (0.14 to 1.55) | | | |
| 10 years | 0.62 (-0.24 to 1.47) | | | |
| 11 years | 1.60 (0.36 to 2.84) | | | |
| 12 years | 1.34 (-0.50 to 3.18) | | | |
| 12.5 years | 1.98 (1.74 to 2.22) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in serum IGF-1 level (nmol/L) from baseline

| | |
|---|---|
| End point title | Mean change in serum IGF-1 level (nmol/L) from baseline |
| End point description: Mean change in serum IGF-1 level (nmol/L) from baseline was reported. | |
| End point type | Secondary |
| End point timeframe: Baseline, 1 year, 2 years, 5 years and 9 years | |

| End point values | Omnitrope | | | |
|---|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 278 | | | |
| Units: nmol/L | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| 1 year | 20.58 (18.77 to 22.39) | | | |
| 2 years | 30.64 (28.16 to 33.12) | | | |
| 5 years | 44.87 (41.33 to 48.40) | | | |
| 9 years | 75.72 (69.59 to 81.85) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in IGFBP-3 levels (nmol/L) from baseline

| | |
|-----------------|--|
| End point title | Mean change in IGFBP-3 levels (nmol/L) from baseline |
|-----------------|--|

| | |
|--|-----------|
| End point description: | |
| Mean change in IGFBP-3 levels (nmol/L) from baseline was reported. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 1 year, 2 years, 5 years and 9 years | |

| End point values | Omnitrope | | | |
|---|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 278 | | | |
| Units: nmol/L | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| 1 year | 30.48 (27.04 to 33.92) | | | |
| 2 years | 48.48 (44.51 to 52.45) | | | |
| 5 years | 92.94 (87.65 to 98.23) | | | |
| 9 years | 139.12 (126.12 to 152.12) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the development of anti-rhGH antibodies during Omnitrope treatment

| | |
|--|--|
| End point title | Number of participants with the development of anti-rhGH antibodies during Omnitrope treatment |
| End point description: | |
| Number of participants with the development of anti-rhGH antibodies with positive test result were reported. | |
| End point type | Secondary |
| End point timeframe: | |
| throughout the study, approximately 13 years | |

| End point values | Omnitrope | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 277 | | | |
| Units: Participants | 23 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment to end of the study i.e. up to 13 years.

Adverse event reporting additional description:

Any signs or symptoms were collected from first dose of study treatment to end of the study i.e. up to 13 years.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 24.1 |

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Omnitrope |
|-----------------------|-----------|

Reporting group description:

All enrolled patients received Omnitrope. The median daily dose varied between 0.0340 and 0.0351 mg/kg/day and the maximum range was 0.000 to 0.040 mg/kg/day over all visits.

| Serious adverse events | Omnitrope | | |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 74 / 277 (26.71%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pachydermodactyly | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|--|--|
| Asthenia | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Face oedema | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Obstruction | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Reproductive system and breast disorders | | | |
| Intermenstrual bleeding | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acquired hydrocele | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Testicular torsion | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Varicocele | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------|--|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Adenoidal hypertrophy | | | |
| subjects affected / exposed | 7 / 277 (2.53%) | | |
| occurrences causally related to treatment / all | 1 / 7 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Asthma | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nasal septum perforation | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Psychiatric disorders | | | |
| Behaviour disorder | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Enuresis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Investigations | | | |
| Cardiac murmur | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Intraocular pressure increased | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Injury, poisoning and procedural complications | | | |
| Abdominal injury | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Head injury | | | |
| subjects affected / exposed | 3 / 277 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Foreign body in gastrointestinal tract | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Joint dislocation | | | |
| subjects affected / exposed | 3 / 277 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Internal injury | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Ligament sprain | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Multiple injuries | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Procedural complication | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Radius fracture | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Road traffic accident | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Skull fracture | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Sternal fracture | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Toxicity to various agents | | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Traumatic shock | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Congenital, familial and genetic disorders | | | |
| Congenital arterial malformation | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Developmental hip dysplasia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gilbert's syndrome | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac disorders | | | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Coma | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------|--|--|
| Intellectual disability | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Headache | | | |
| subjects affected / exposed | 3 / 277 (1.08%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Seizure | | | |
| subjects affected / exposed | 3 / 277 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Syncope | | | |
| subjects affected / exposed | 3 / 277 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Blood and lymphatic system disorders | | | |
| Lymphadenitis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Ear and labyrinth disorders | | | |
| Tympanic membrane perforation | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------|--|--|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 277 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Chronic gastritis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Eosinophilic oesophagitis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Inguinal hernia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 277 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Malabsorption | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Vitiligo | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------|--|--|
| Urethral fistula | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urethral stenosis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Endocrine disorders | | | |
| Precocious puberty | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Scoliosis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------------------------|--|--|
| Infections and infestations Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 4 / 277 (1.44%) 0 / 4 0 / 1 | | |
| Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 277 (0.72%) 0 / 2 0 / 1 | | |
| Bacterial sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 277 (0.36%) 0 / 1 0 / 1 | | |
| Ear infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 277 (0.36%) 0 / 1 0 / 1 | | |
| Epididymitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 277 (0.36%) 0 / 2 0 / 1 | | |
| Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 3 / 277 (1.08%) 0 / 4 0 / 1 | | |
| Giardiasis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 277 (0.36%) 0 / 1 0 / 1 | | |
| Helicobacter infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 277 (0.72%) 0 / 2 0 / 1 | | |
| Infectious mononucleosis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Laryngitis | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Orchitis | | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Otitis media | | | | |
| subjects affected / exposed | 4 / 277 (1.44%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Otitis media acute | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Otitis media chronic | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Peritonitis | | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pharyngitis | | | | |
| subjects affected / exposed | 2 / 277 (0.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pneumonia | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 277 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

Frequency threshold for reporting non-serious adverse events: 3 %

| | | | |
|---|--------------------|--|--|
| Non-serious adverse events | Omnitrope | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 210 / 277 (75.81%) | | |
| Investigations | | | |
| Insulin-like growth factor increased | | | |
| subjects affected / exposed | 9 / 277 (3.25%) | | |
| occurrences (all) | 16 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 27 / 277 (9.75%) | | |
| occurrences (all) | 49 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 23 / 277 (8.30%) | | |
| occurrences (all) | 42 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 11 / 277 (3.97%) | | |
| occurrences (all) | 16 | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 9 / 277 (3.25%) | | |
| occurrences (all) | 12 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 277 (3.61%) | | |
| occurrences (all) | 18 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 10 / 277 (3.61%) | | |
| occurrences (all) | 10 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 21 / 277 (7.58%) | | |
| occurrences (all) | 27 | | |
| Vomiting | | | |
| subjects affected / exposed | 13 / 277 (4.69%) | | |
| occurrences (all) | 24 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|--------------------------|--|--|
| Cough subjects affected / exposed occurrences (all) | 20 / 277 (7.22%) 56 | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 14 / 277 (5.05%) 26 | | |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 12 / 277 (4.33%) 15 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 27 / 277 (9.75%) 32 | | |
| Musculoskeletal and connective tissue disorders Scoliosis subjects affected / exposed occurrences (all) | 12 / 277 (4.33%) 12 | | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 58 / 277 (20.94%) 104 | | |
| Ear infection subjects affected / exposed occurrences (all) | 14 / 277 (5.05%) 22 | | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 11 / 277 (3.97%) 12 | | |
| Influenza subjects affected / exposed occurrences (all) | 11 / 277 (3.97%) 12 | | |
| Laryngitis subjects affected / exposed occurrences (all) | 9 / 277 (3.25%) 15 | | |
| Nasopharyngitis | | | |

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|-----------------------------------|-------------------|--|--|
| subjects affected / exposed | 78 / 277 (28.16%) | | |
| occurrences (all) | 302 | | |
| Otitis media | | | |
| subjects affected / exposed | 19 / 277 (6.86%) | | |
| occurrences (all) | 35 | | |
| Otitis media acute | | | |
| subjects affected / exposed | 9 / 277 (3.25%) | | |
| occurrences (all) | 13 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 92 / 277 (33.21%) | | |
| occurrences (all) | 310 | | |
| Rhinitis | | | |
| subjects affected / exposed | 20 / 277 (7.22%) | | |
| occurrences (all) | 33 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 25 / 277 (9.03%) | | |
| occurrences (all) | 39 | | |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 277 (6.14%) | | |
| occurrences (all) | 21 | | |
| Scarlet fever | | | |
| subjects affected / exposed | 11 / 277 (3.97%) | | |
| occurrences (all) | 12 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 47 / 277 (16.97%) | | |
| occurrences (all) | 119 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 35 / 277 (12.64%) | | |
| occurrences (all) | 86 | | |
| Sinusitis | | | |
| subjects affected / exposed | 15 / 277 (5.42%) | | |
| occurrences (all) | 17 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 17 / 277 (6.14%) | | |
| occurrences (all) | 20 | | |
| Varicella | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 37 / 277 (13.36%) | | |
| occurrences (all) | 38 | | |
| Viral infection | | | |
| subjects affected / exposed | 18 / 277 (6.50%) | | |
| occurrences (all) | 29 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 August 2007 | <ul style="list-style-type: none">- Change from EP2000 5 mg/ml lyophilized powder for solution for injection to EP2000 5 mg/1.5ml solution for injection- Reduction of blood glucose measurements- Recording of historical IGF-1 and IGFBP-3 |
| 27 November 2008 | <ul style="list-style-type: none">- Inclusion of subgroup analysis for different formulations- Allowing treatment of overweight children with SGA (deletion of exclusion criterion 7)- Safety reporting for device related events- Clarification of BA determination procedure |
| 22 March 2012 | <ul style="list-style-type: none">- Introduction of a higher Omnitrope dose strength (10 mg/1.5 mL)- Discontinuation of anti-HCP antibody assessment |
| 24 August 2017 | <ul style="list-style-type: none">- Addition of instructions for female patients of childbearing potential- Changes due to implementation of new processes and a new protocol template by the sponsor- Removal of the per-protocol population from analysis |
| 07 February 2020 | <ul style="list-style-type: none">- The post-treatment observation EP00-402 (for patients who had been treated within this study, EP00-401) was terminated in 2018. All references to study EP00-402 were removed- Clarification of the lost to follow up definition to limit protocol deviations and facilitate compliance to visit schedule |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported