



Clinical trial results:

Safety and dose finding study of different MOD-4023 dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-004553-60 |
| Trial protocol | HU SK CZ GR PL BG |
| Global end of trial date | 16 November 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 03 July 2025 |
| First version publication date | 03 July 2025 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | CP-4-004 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01592500 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | OPKO Biologics Ltd. |
| Sponsor organisation address | Ashlagan 16, Kiryat Gat, Israel, 8211804 |
| Public contact | OPKO Health, Inc., OPKO Health, Inc., 305 5754100, contact@opko.com |
| Scientific contact | OPKO Health, Inc., OPKO Health, Inc., 305 5754100, contact@opko.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? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 November 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 July 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the safety, efficacy and tolerability of three MOD-4023 doses to that of a commercially available standard daily recombinant human growth hormone (r-hGH) formulation, in pre-pubertal children with growth failure due to insufficient secretion of endogenous growth hormone.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) GCP Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study participants.

Investigator signature of the protocol indicates their commitment to perform study activities as outlined in the protocol, and to ensure that all personnel partaking in any study related activity are adequately trained.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 18 June 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | United States: 2 |
| Country: Number of subjects enrolled | Belarus: 13 |
| Country: Number of subjects enrolled | Ukraine: 14 |
| Country: Number of subjects enrolled | Russian Federation: 16 |
| Country: Number of subjects enrolled | Bulgaria: 4 |
| Country: Number of subjects enrolled | Greece: 2 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Worldwide total number of subjects | 53 |
| EEA total number of subjects | 8 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 53 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 56 patients from 14 centers in seven countries were randomized in the study. Three patients were randomized and withdrew consent prior to receiving any study medication. Fifty-three patients (17 female and 36 male) were enrolled and received study investigational medication or Genotropin.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Main Study |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | MOD-4023 Low Dose |

Arm description:

0.25 mg MOD-4023 protein/kg/week

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MOD-4023 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Once weekly subcutaneous injection of long acting r-hGH (MOD-4023)

| | |
|------------------|----------------------|
| Arm title | MOD-4023 Middle Dose |
|------------------|----------------------|

Arm description:

0.48 mg MOD-4023 protein/kg/week

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MOD-4023 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Once weekly subcutaneous injection of long acting r-hGH (MOD-4023)

| | |
|------------------|--------------------|
| Arm title | MOD-4023 High Dose |
|------------------|--------------------|

Arm description:

0.66 mg MOD-4023 protein/kg/week

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MOD-4023 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Once weekly subcutaneous injection of long acting r-hGH (MOD-4023)

| | |
|--|--|
| Arm title | Genotropin |
| Arm description: Genotropin: 0.034 mg/kg/day. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Genotropin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Once daily subcutaneous injection of Somatropin (r-hGH; Genotropin)

| Number of subjects in period 1 | MOD-4023 Low Dose | MOD-4023 Middle Dose | MOD-4023 High Dose |
|---------------------------------------|-------------------|----------------------|--------------------|
| Started | 13 | 15 | 14 |
| Completed | 13 | 15 | 14 |

| Number of subjects in period 1 | Genotropin |
|---------------------------------------|------------|
| Started | 11 |
| Completed | 11 |

Period 2

| | |
|------------------------------|------------------------------|
| Period 2 title | MOD-4023 OLE and PEN Periods |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|---|--|
| Arm title | MOD-4023 OLE and PEN-OLE Periods |
| Arm description: Once weekly injection of long acting r-hGH (MOD-4023) provided as a solution for injection containing 20 or 50 mg/mL MOD-4023 in a single patient use, multi-dose, disposable pre-filled pen (PEN). | |
| Arm type | Experimental |
| Investigational medicinal product name | MOD-4023 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Once weekly injection of long acting r-hGH (MOD-4023) provided as a solution for injection containing 20 or 50 mg/mL MOD-4023 in a single patient use, multi-dose, disposable pre-filled pen (PEN).

| Number of subjects in period 2^[1] | MOD-4023 OLE and PEN-OLE Periods |
|---|---|
| Started | 48 |
| Completed | 21 |
| Not completed | 27 |
| Consent withdrawn by subject | 15 |
| Adverse event, non-fatal | 3 |
| Due to war activities in the country | 1 |
| Lost to follow-up | 2 |
| Final height achieved | 5 |
| Protocol deviation | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 5 subjects who completed the Main period did not consent to OLE year 1

Baseline characteristics

Reporting groups

| | |
|------------------------------|----------------------------------|
| Reporting group title | MOD-4023 Low Dose |
| Reporting group description: | 0.25 mg MOD-4023 protein/kg/week |
| Reporting group title | MOD-4023 Middle Dose |
| Reporting group description: | 0.48 mg MOD-4023 protein/kg/week |
| Reporting group title | MOD-4023 High Dose |
| Reporting group description: | 0.66 mg MOD-4023 protein/kg/week |
| Reporting group title | Genotropin |
| Reporting group description: | Genotropin: 0.034 mg/kg/day. |

| Reporting group values | MOD-4023 Low Dose | MOD-4023 Middle Dose | MOD-4023 High Dose |
|--|-------------------|----------------------|--------------------|
| Number of subjects | 13 | 15 | 14 |
| 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) | 13 | 15 | 14 |
| 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 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 6 | 5 |
| Male | 10 | 9 | 9 |

| Reporting group values | Genotropin | Total | |
|--|------------|-------|--|
| Number of subjects | 11 | 53 | |
| 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) | 11 | 53 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |

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

| | | | |
|---------------------------------------|---|----|--|
| Gender categorical Units: Subjects | | | |
| Female | 3 | 17 | |
| Male | 8 | 36 | |

End points

End points reporting groups

| | |
|-----------------------------------|---|
| Reporting group title | MOD-4023 Low Dose |
| Reporting group description: | 0.25 mg MOD-4023 protein/kg/week |
| Reporting group title | MOD-4023 Middle Dose |
| Reporting group description: | 0.48 mg MOD-4023 protein/kg/week |
| Reporting group title | MOD-4023 High Dose |
| Reporting group description: | 0.66 mg MOD-4023 protein/kg/week |
| Reporting group title | Genotropin |
| Reporting group description: | Genotropin: 0.034 mg/kg/day. |
| Reporting group title | MOD-4023 OLE and PEN-OLE Periods |
| Reporting group description: | Once weekly injection of long acting r-hGH (MOD-4023) provided as a solution for injection containing 20 or 50 mg/mL MOD-4023 in a single patient use, multi-dose, disposable pre-filled pen (PEN). |
| Subject analysis set title | MOD-4023 OLE Year 1 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | Subjects entered MOD-4023 OLE Year 1 |
| Subject analysis set title | MOD-4023 OLE Year 2 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | Subjects entered MOD-4023 OLE Year 2 |
| Subject analysis set title | MOD-4023 OLE Year 3 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | Subjects entered MOD-4023 OLE Year 3 |
| Subject analysis set title | MOD-4023 OLE Year 4 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | Subjects entered MOD-4023 OLE Year 4 |
| Subject analysis set title | MOD-4023 PEN Year 1 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | Subjects entered MOD-4023 PEN Year 1 |
| Subject analysis set title | MOD-4023 PEN Year 2 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | Subjects entered MOD-4023 PEN Year 2 |
| Subject analysis set title | MOD-4023 PEN Year 3 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | Subjects entered MOD-4023 PEN Year 3 |
| Subject analysis set title | MOD-4023 PEN Year 4 |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Subjects entered MOD-4023 PEN Year 4

| | |
|----------------------------|---------------------|
| Subject analysis set title | MOD-4023 PEN Year 5 |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Subjects entered MOD-4023 PEN Year 5

Primary: Annual Height Velocity at 12 months

| | |
|-----------------|--|
| End point title | Annual Height Velocity at 12 months ^[1] |
|-----------------|--|

End point description:

Annual Height Velocity in cm/year measured after 12 months of treatment

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

End point timeframe:

12 months of treatment

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 statistics, with mean, standard deviation, range, count and confidence intervals was used to present the results.

| End point values | MOD-4023 Low Dose | MOD-4023 Middle Dose | MOD-4023 High Dose | Genotropin |
|--------------------------------------|-------------------|----------------------|--------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13 | 15 | 13 | 11 |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 10.4 (± 2.6) | 11.0 (± 2.3) | 11.9 (± 3.5) | 12.5 (± 2.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: Height Velocity at 6 months

| | |
|-----------------|-----------------------------|
| End point title | Height Velocity at 6 months |
|-----------------|-----------------------------|

End point description:

Annualized Height Velocity in cm/year measured after 6 months of treatment

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

End point timeframe:

After 6 months of treatment

| End point values | MOD-4023 Low Dose | MOD-4023 Middle Dose | MOD-4023 High Dose | Genotropin |
|--------------------------------------|-------------------|----------------------|--------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13 | 15 | 13 | 11 |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 11.8 (± 3.6) | 12.5 (± 2.4) | 13.5 (± 5.0) | 15.0 (± 2.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Height Standard Deviation Score (SDS)

End point title | Change in Height Standard Deviation Score (SDS)

End point description:

Change in height standard deviation score from baseline (compared to normal population of same age group and sex). Height SDS was calculated as height minus reference mean height divided by SD of the reference mean height

End point type | Secondary

End point timeframe:

After 6 and 12 months of treatment

| End point values | MOD-4023 Low Dose | MOD-4023 Middle Dose | MOD-4023 High Dose | Genotropin |
|--------------------------------------|-------------------|----------------------|--------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13 | 15 | 13 | 11 |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | | | | |
| After 6 months of treatment | 0.65 (± 0.36) | 0.75 (± 0.25) | 0.90 (± 0.39) | 1.00 (± 0.35) |
| After 12 months of treatment | 1.09 (± 0.53) | 1.19 (± 0.49) | 1.45 (± 0.61) | 1.51 (± 0.47) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IGF-1 Standard Deviation Score

End point title | Change in IGF-1 Standard Deviation Score

End point description:

Change in IGF-1 standard deviation score from reference population mean of same age group and sex (WHO source). IGF-1 SDS was calculated as IGF-1 result minus reference mean IGF-1 result divided by SD of the reference mean IGF-1 value.

End point type | Secondary

End point timeframe:

Once monthly on day 4 after the last dose

| End point values | MOD-4023 Low Dose | MOD-4023 Middle Dose | MOD-4023 High Dose | Genotropin |
|--------------------------------------|-------------------|----------------------|--------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13 | 15 | 14 | 11 |
| Units: microgram(s)/litre | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit1/ Week 1 | -1.86 (± 0.817) | -1.94 (± 0.899) | -2.13 (± 0.887) | -2.12 (± 0.813) |
| Visit 5/ Week 10 | -1.03 (± 0.902) | -0.279 (± 0.891) | -0.001 (± 1.164) | -0.515 (± 1.238) |
| Visit 6 / Week 14 | -1.07 (± 0.553) | -0.275 (± 0.772) | -0.058 (± 1.067) | -0.557 (± 1.216) |
| Visit 7 / Week 18 | -0.815 (± 0.733) | 0.189 (± 0.707) | -0.083 (± 1.299) | -0.310 (± 0.896) |
| Visit 8 / Week 22 | -0.958 (± 0.673) | -0.188 (± 0.684) | 0.023 (± 0.964) | -0.495 (± 1.108) |
| Visit 9 / Week 23 | -1.70 (± 0.741) | -1.48 (± 0.653) | -1.47 (± 0.865) | 0 (± 0) |
| Visit 10 / Week 26 | -0.725 (± 0.801) | 0.088 (± 0.803) | -0.011 (± 1.084) | -0.235 (± 0.919) |
| Visit 11 / Month 9 | -0.119 (± 0.921) | 0.184 (± 0.905) | 0.261 (± 1.108) | 0.124 (± 1.071) |
| Visit 12 / Month 12 | -0.458 (± 1.194) | -0.029 (± 1.296) | 0.358 (± 0.709) | -0.015 (± 1.485) |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Annual Height Velocity OLE

| | |
|------------------------|--|
| End point title | Annual Height Velocity OLE |
| End point description: | A summary of the annualized HV at the end of each year for Periods III/IV (OLE Years 1 - 4) and V (PEN Years 1 - 5). |
| End point type | Other pre-specified |
| End point timeframe: | 8 years |

| End point values | MOD-4023 OLE Year 1 | MOD-4023 OLE Year 2 | MOD-4023 OLE Year 3 | MOD-4023 OLE Year 4 |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 46 | 43 | 38 | 1 |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 7.99 (± 1.54) | 7.46 (± 1.35) | 7.12 (± 1.66) | 4.63 (± 0) |

| End point values | MOD-4023 PEN Year 1 | MOD-4023 PEN Year 2 | MOD-4023 PEN Year 3 | MOD-4023 PEN Year 4 |
|-------------------------|---------------------|---------------------|---------------------|---------------------|
|-------------------------|---------------------|---------------------|---------------------|---------------------|

| | | | | |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 35 | 31 | 26 | 19 |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 6.96 (± 1.89) | 6.37 (± 2.12) | 5.31 (± 1.368) | 6.05 (± 1.74) |

| | | | | |
|--------------------------------------|------------------------|--|--|--|
| End point values | MOD-4023 PEN Year 5 | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 2 | | | |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 6.31 (± 0.41) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Delta Height SDS OLE

| | |
|------------------------|--|
| End point title | Delta Height SDS OLE |
| End point description: | A summary of annual change in height SDS at the end of each year for Periods III/IV (OLE Years 1 - 4) and V (PEN Years 1 - 5). |
| End point type | Other pre-specified |
| End point timeframe: | 8 years |

| | | | | |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| End point values | MOD-4023 OLE Year 1 | MOD-4023 OLE Year 2 | MOD-4023 OLE Year 3 | MOD-4023 OLE Year 4 |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 46 | 43 | 38 | 1 |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 0.57 (± 0.34) | 0.40 (± 0.28) | 0.34 (± 0.28) | 0.09 (± 0) |

| | | | | |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| End point values | MOD-4023 PEN Year 1 | MOD-4023 PEN Year 2 | MOD-4023 PEN Year 3 | MOD-4023 PEN Year 4 |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 35 | 31 | 26 | 19 |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 0.27 (± 0.25) | 0.21 (± 0.29) | 0.10 (± 0.21) | 0.18 (± 0.34) |

| | | | | |
|--------------------------------------|------------------------|--|--|--|
| End point values | MOD-4023 PEN Year 5 | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 2 | | | |
| Units: centimetre | | | | |
| arithmetic mean (standard deviation) | 0.07 (± 0.13) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of IGF-1 SDS levels OLE

| | |
|------------------------|--|
| End point title | Summary of IGF-1 SDS levels OLE |
| End point description: | A summary of IGF-I SDS at the end of each year for Periods III/IV (OLE Years 1 - 4) and V (PEN Years 1 - 5). |
| End point type | Other pre-specified |
| End point timeframe: | 8 years |

| | | | | |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| End point values | MOD-4023 OLE Year 1 | MOD-4023 OLE Year 2 | MOD-4023 OLE Year 3 | MOD-4023 OLE Year 4 |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 43 | 41 | 38 | 1 |
| Units: microgram(s)/litre | | | | |
| arithmetic mean (standard deviation) | 0.64 (± 0.96) | 0.65 (± 1.08) | 1.05 (± 0.82) | 0.29 (± 0) |

| | | | | |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| End point values | MOD-4023 PEN Year 1 | MOD-4023 PEN Year 2 | MOD-4023 PEN Year 3 | MOD-4023 PEN Year 4 |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 35 | 31 | 26 | 18 |
| Units: microgram(s)/litre | | | | |
| arithmetic mean (standard deviation) | 1.29 (± 0.81) | 0.96 (± 1.15) | 0.86 (± 0.89) | 1.00 (± 0.68) |

| | | | | |
|--------------------------------------|------------------------|--|--|--|
| End point values | MOD-4023 PEN Year 5 | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 2 | | | |
| Units: microgram(s)/litre | | | | |
| arithmetic mean (standard deviation) | 1.45 (± 0.33) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period for collecting adverse events begins after signing the informed consent form and continues until 4 weeks after the patient has received the last dose of study treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | MOD-4023 Low Dose - Main Study |
|-----------------------|--------------------------------|

Reporting group description:

0.25 mg MOD-4023 protein/kg/week equivalent to 0.18 mg hGH/kg weekly injection

| | |
|-----------------------|-----------------------------------|
| Reporting group title | MOD-4023 Middle Dose - Main Study |
|-----------------------|-----------------------------------|

Reporting group description:

0.48 mg MOD-4023 protein/kg/week equivalent to 0.35 mg hGH/kg weekly injection.

| | |
|-----------------------|---------------------------------|
| Reporting group title | MOD-4023 High Dose - Main Study |
|-----------------------|---------------------------------|

Reporting group description:

0.66 mg MOD-4023 protein/kg/week equivalent to 0.48 mg hGH/kg weekly injection.

| | |
|-----------------------|-------------------------|
| Reporting group title | Genotropin - Main Study |
|-----------------------|-------------------------|

Reporting group description:

Genotropin: 0.034 mg/kg/day

| | |
|-----------------------|---------------------|
| Reporting group title | MOD-4023 OLE Period |
|-----------------------|---------------------|

Reporting group description: -

| Serious adverse events | MOD-4023 Low Dose - Main Study | MOD-4023 Middle Dose - Main Study | MOD-4023 High Dose - Main Study |
|---|--------------------------------|-----------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Schwannoma | | | |
| alternative dictionary used: MedDRA 20.1 | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastric disorder | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Scoliosis | | | |
| alternative dictionary used: MedDRA 20.1 | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Thyroid gland abscess | | | |
| alternative dictionary used: MedDRA 20.1 | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Genotropin - Main Study | MOD-4023 OLE Period | |
|--|-------------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 4 / 48 (8.33%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Schwannoma | | | |
| alternative dictionary used: MedDRA 20.1 | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Scoliosis | | | |

| | | | |
|--|----------------|----------------|--|
| alternative dictionary used: MedDRA 20.1 | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Thyroid gland abscess | | | |
| alternative dictionary used: MedDRA 20.1 | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | MOD-4023 Low Dose - Main Study | MOD-4023 Middle Dose - Main Study | MOD-4023 High Dose - Main Study |
|--|-----------------------------------|--------------------------------------|------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 13 (76.92%) | 10 / 15 (66.67%) | 10 / 14 (71.43%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site erythema | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Injection site haematoma | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Injection site pain | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 5 |
| Injection site pruritus | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Injection site swelling | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 2 |
| Edema Peripheral | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site bruising | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 15 (6.67%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Snoring | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oropharyngeal pain | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Psychiatric disorders Attention deficit hyperactivity disorder subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Investigations Body temperature increased subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Hemoglobin Decreased subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Insulin-like growth factor increased subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Red blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Thyroxine decreased subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Injury, poisoning and procedural complications Accidental overdose subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Meniscus cyst subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Clavicle fracture subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Nervous system disorders | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| Headache subjects affected / exposed occurrences (all) | 4 / 13 (30.77%) 6 | 1 / 15 (6.67%) 3 | 0 / 14 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 2 / 15 (13.33%) 2 | 3 / 14 (21.43%) 4 |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Eye disorders Amblyopia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Astigmatism subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Eye inflammation subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Eyelid oedema subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 8 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Hypermetropia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Myopia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Gastrointestinal disorders | | | |

| | | | |
|--|----------------|----------------|----------------|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Acetonaemic vomiting | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Enteritis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Biliary dyskinesia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sphincter of Oddi dysfunction | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Petechiae | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urticaria | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Renal and urinary disorders Hematuria subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 2 | 1 / 15 (6.67%) 1 | 1 / 14 (7.14%) 1 |
| Secondary adrenocortical insufficiency subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 |
| Delayed puberty subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Secondary hypogonadism subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Connective tissue disorder subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Scoliosis | | | |

| | | | |
|------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteochondrosis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| acute tonsillitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Helminthic infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 6 | 3 | 0 |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 1 / 15 (6.67%) | 2 / 14 (14.29%) |
| occurrences (all) | 7 | 1 | 2 |

| | | | |
|---|---------------------|----------------------|----------------------|
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 2 / 15 (13.33%) 2 | 1 / 14 (7.14%) 1 |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Tracheitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 |
| Tracheobronchitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 |
| Varicella subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 2 / 14 (14.29%) 2 |
| Viral infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 |
| Tonsillitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Corona virus infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Hand-foot-and-mouth disease subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Lower respiratory tract infection viral subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Pharyngitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Rotavirus infection subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Impaired fasting glucose subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Obesity subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 |

| Non-serious adverse events | Genotropin - Main Study | MOD-4023 OLE Period | |
|--|-------------------------|---------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 8 / 11 (72.73%) | 42 / 48 (87.50%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|----------------|----------------|--|
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) | |
| occurrences (all) | 0 | 2 | |
| Injection site haematoma | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injection site pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injection site pruritus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injection site swelling | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Edema Peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 4 / 48 (8.33%) | |
| occurrences (all) | 1 | 7 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injection site bruising | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 48 (4.17%) 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 48 (6.25%) | |
| occurrences (all) | 0 | 6 | |
| Snoring | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) | |
| occurrences (all) | 0 | 3 | |
| Psychiatric disorders | | | |
| Attention deficit hyperactivity disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hemoglobin Decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Insulin-like growth factor increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Red blood cell count decreased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thyroxine decreased | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 48 (0.00%) 0 | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Meniscus cyst subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Clavicle fracture subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 48 (4.17%) 2 | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 4 / 48 (8.33%) 6 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 48 (0.00%) 0 | |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 48 (4.17%) 2 | |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 48 (0.00%) 0 | |
| Eye disorders | | | |
| Amblyopia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Astigmatism | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eye inflammation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypermetropia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myopia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) | |
| occurrences (all) | 0 | 2 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 48 (4.17%) | |
| occurrences (all) | 1 | 2 | |
| Acetonaemic vomiting | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Toothache | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---------------------|---------------------|--|
| Vomiting subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 3 / 48 (6.25%) 3 | |
| Hepatobiliary disorders Biliary dyskinesia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Sphincter of Oddi dysfunction subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Petechiae subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Renal and urinary disorders Hematuria subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 2 / 48 (4.17%) 4 | |
| Secondary adrenocortical insufficiency subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Delayed puberty | | | |

| | | | |
|--|----------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 3 / 48 (6.25%) 3 | |
| Secondary hypogonadism subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 48 (4.17%) 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 3 / 48 (6.25%) 6 | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Connective tissue disorder subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 2 / 48 (4.17%) 4 | |
| Scoliosis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 3 / 48 (6.25%) 6 | |
| Osteochondrosis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 48 (4.17%) 2 | |
| Infections and infestations | | | |
| acute tonsillitis subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 48 (0.00%) 0 | |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 11 / 48 (22.92%) 21 | |
| Cystitis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Ear infection | | | |

| | | |
|-----------------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 4 / 48 (8.33%) |
| occurrences (all) | 0 | 4 |
| Fungal skin infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gastroenteritis | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Helminthic infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Nasopharyngitis | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 7 / 48 (14.58%) |
| occurrences (all) | 3 | 19 |
| Pulpitis dental | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) |
| occurrences (all) | 1 | 0 |
| Respiratory tract infection | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 2 / 48 (4.17%) |
| occurrences (all) | 7 | 5 |
| Respiratory tract infection viral | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 48 (4.17%) |
| occurrences (all) | 1 | 3 |
| Rhinitis | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 7 / 48 (14.58%) |
| occurrences (all) | 1 | 18 |
| Sinusitis | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 48 (0.00%) |
| occurrences (all) | 1 | 0 |
| Tracheitis | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Tracheobronchitis | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 0 | 0 |
| Varicella | | |

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|---|----------------|------------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 5 / 48 (10.42%) |
| occurrences (all) | 0 | 5 |
| Viral infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 48 (6.25%) |
| occurrences (all) | 0 | 5 |
| Tonsillitis | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 5 / 48 (10.42%) |
| occurrences (all) | 1 | 6 |
| Upper respiratory tract infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 13 / 48 (27.08%) |
| occurrences (all) | 0 | 44 |
| Viral upper respiratory tract infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 5 / 48 (10.42%) |
| occurrences (all) | 0 | 7 |
| Pneumonia | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 48 (6.25%) |
| occurrences (all) | 0 | 3 |
| Corona virus infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 0 | 2 |
| Hand-foot-and-mouth disease | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 0 | 2 |
| Lower respiratory tract infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 0 | 5 |
| Lower respiratory tract infection viral | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 0 | 2 |
| Pharyngitis | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 0 | 2 |
| Rotavirus infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 48 (4.17%) |
| occurrences (all) | 0 | 2 |
| Conjunctivitis | | |

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|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 48 (4.17%) 2 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Impaired fasting glucose | | | |
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 48 (0.00%) 0 | |
| Obesity | | | |
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 48 (4.17%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 04 April 2012 | <ol style="list-style-type: none">1 Principal Investigator was changed to read Coordinating Investigator2 Maximum number of participating countries updated3 Rotation of the injection site updated4 The Screening period was extended to six weeks5 The assessment for anti-MOD-4023 Abs removed from Screening6 Clarify the stratification7 Assessment of Baseline MOD-4023 (Cohorts 1-3)8 An HbA1c assessment was added to Visits 4, 11, 129 Protocol was amended to remove inclusion criterion number 510 The interval between two HT measurements was clarified11 Karyotype testing was specified to be performed by central laboratory12 The planned PK/PD analyses were amended13 Clarify that MOD-4023 was tested in adults in a Phase II14 The allocation of identification numbers was clarified16 Assessment of parameters of glucose metabolism in Genotropin patients, at Visits 2 and 4 added17 Clarify that Lp(a) assessment will be done only at Visit 618 Clarify that the final visit will occur four days (-1) after the last MOD-4023 dose for Cohorts 1-3 and the day after the last Genotropin dose for Cohort 419 Clarify that predicted adult age will be calculated for children above seven years20 Coordinating Investigator will approval the use of thyroid replacement therapy21 Clarify that deviations in the weekly dosing during the PK/PD period will be considered as major22 Clarify that the reporting of SAEs will be done electronically23 Change in the contact person for SAE reporting24 Address the possibility of measurement of cortisol levels is a glucagon stimulation test was historically25 Clarify that both GH-stimulation tests were not required to have been conducted by the central laboratory26 Clarify that a screening, and not a Baseline adrenocorticotrophic hormone (ACTH) test will be done27 Clarify that a cubital vein will be used for the ACTH test28 Replace the Wong-Baker image for local pain29 list the names of the central technical facilities and contractors was amende |

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| 26 June 2012 | <p>No patients were enrolled at the time this amendment was issued</p> <ol style="list-style-type: none"> 1. Redefine the content of the study drug through the addition of "growth hormone" or "protein" where applicable. 2. Clarification was made on sex hormone priming 3. The protocol was amended to modify the expression of the doses in the in the three MOD-4023 cohorts due to a change in the calculation of content of the drug. 4. The protocol was amended to include the possibility accepting results from historical sex hormone stimulation testing to avoid the need to retest children in a short time frame. At least one of the two tests, however, must be retested at the central laboratory and as such, reserve samples must have been retained at the original testing facility. If a patient requires both stimulation tests during Screening, it is recommended that testing be performed on two consecutive days. 5. The definition of malnourishment was clarified to be inclusive of all three indicating factors: serum albumin below LLN according to the reference ranges of the central laboratory, serum iron below the LLN according to reference ranges of the central lab, and BMI < -2SD for age and sex. 6. Clarify the primary efficacy endpoint of annual HV in cm/year at 12 months 7. Correct the molecular weight of the IP to correctly read ~38,330 Daltons (Da). 8. Change the lowest chosen dose of MOD-4023 due to the modified content of the IP. 9. Clarify that the primary endpoint is Annual HV at 12 months. 10. Clarify that all patients, regardless of the MOD-4023 cohort to which they are assigned, will begin treatment at the lowest dose. Dose levels will then be increased in a step wise manner until the maximum dose is obtained. 11. Define the assay that will be used for IGF-1 assessment. 12. Protocol was amended to describe the procedure of sex hormone priming that will be performed prior to GH-stimulation tests |
| 20 March 2013 | <p>At the time this amendment was issued eight patients had been treated.</p> <ol style="list-style-type: none"> 1. Protocol was amended to include additional sites. 2. Distribution of study population to address change in inclusion criteria 2: Patients will be divided into two subgroups: Up to 40 patients with ppGH levels after stimulation test ≤ 7 ng/ml and up to 16 patients with ppGH levels after stimulation test > 7 and ≤ 10 ng/ml. 3. The protocol was amended to address change in ppGH level to address the known common practice in newly added countries and already participating sites in the study. 4. Protocol was amended to address change in study population; sub-groups of ≤ 7 ng/ml and > 7 ng/ml and ≤ 10 ng/ml. 5. The protocol was amended to reflect the current practice for glucagon testing to avoid unnecessary side effects. 6. The list of central laboratories was updated. 7. The protocol was amended to clarify the analysis of efficacy: <ol style="list-style-type: none"> a. The efficacy analysis will be performed based upon the FAS and PP subsets and subgroups based on peak hGH level following stimulation tests. 8. Protocol was amended to clarify GH stimulation tests and other assessments would be performed per the 2000 Growth Hormone Research Society Consensus Guidelines. 9. The glucagon test was amended to reflect the current practice for the test and to avoid unnecessary side-effects for the patients. |

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| 23 July 2013 | <p>At the time of this amendment 32 patients had been treated.</p> <ol style="list-style-type: none"> 1. The protocol was amended to address a change concerning stratification factors since the previous ones resulted in an unequal distribution of patients with regards to [HTSDS - target HTSDS] and ppGH levels. Including this new factor, all new patients will be randomized using the same dynamic minimization rule while considering the following stratification factors and using the allocation of the existing patients as the baseline for determining the allocation of new patients. Moreover, this will neither modify the allocation of existing patients, nor create a situation where a patient that would have been eligible based on the inclusion/exclusion criteria will not be included solely based on the randomization parameters, nor the Investigator's ability to predict the next dose allocation (and therefore his judgment whether to include a patient in the study or not). All eligible patients will be enrolled per protocol. 2. The protocol was amended to address a change to mistakenly specified dose levels of lower dose cohorts (change to 0.48 and 0.66 from 0.31 and 0.60). This was an editorial change to the protocol to clarify the doses that were actually taken. 3. The protocol was amended to address a change within section "Contact persons and numbers" and mistakenly left wrong address. 4. Visit schedule was updated to reflect \leqsix weeks acceptable for Screening. |
| 01 September 2013 | <p>At the time of this amendment, 53 patients had been treated.</p> <ol style="list-style-type: none"> 1. Amendment done to focus and highlight inclusion criteria for the OLE study 2. The duration of the OLE was clarified as being expected to run for a 12 month duration. 3. The process for distributing MOD-4023 to patients in the OLE was clarified 4. Address the change in stratification methodology to the dynamic minimization method. Further stratification for ppGH levels (≤ 2, $2 < \text{ppGH} \leq 7$) was introduced such that patients with ppGH levels $> 7-10$ were permitted to be enrolled, however, these patients would have a separate randomization list. 5. Fully describe the OLE period including decisions regarding assessment of eligibility, randomization, allocation of study drug, and study visit design. 6. Clarification made within the protocol, the reference to last visit refers only to the Main Study and does not include the OLE. When all patients have completed the Main Study, a full-analysis (CSR) will be performed based on the SAP. When all patients complete the second year of treatment, an additional analysis will be performed. 7. The protocol was amended to clarify that dose efficacy will be analyzed after 12 months of treatment on a per patient basis. Patients who had not successfully achieved the minimally satisfactorily growth rate were moved to the next higher dose level. 8. Specify the dose level that will be used in the OLE period. 9. Specify randomization for the Main Study and OLE such that all patients will receive MOD-4023 either at the dose level they had received during the Main Study, or will be randomized to one of the three MOD-4023 cohort if they had been receiving placebo during the Main Study. 10. Specify the way of analyzing the dose and efficacy within both Main Study and OLE; dose efficacy will be analyzed again after 12 months of treatment on an individual patient level. 11. The list of central laboratories was updated. |

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| 26 January 2015 | <p>The following changes were made to the protocol:</p> <ul style="list-style-type: none"> • The protocol was amended to remove the study site "Bulgaria" from the extension study. • Updated the duration of the main study from 24 months to 12 months for each subject and the OLE period was based on the initial extension of 12 months of active treatment for all subjects completing the main study which was extended on a yearly basis until marketing approval in each country. • Study design and procedures were revised to indicate that all subjects who completed 12 months of the main study and those who were already in the LT-OLE period were eligible to continue in the extension study until marketing approval in their country, subject to an annual notification to local IEC/IRB continuation of the study. In both cases, subjects were to sign the new assent and/or ICD. • OLE was divided into first year extension with 12 months continuous repeated dosing of somatrogon. Provided dose reduction paradigm based on IGF-1 SDS for subjects switching to 0.66 mg/kg/week somatrogon. • Clarification was added that the end of study was identical to Visit 12 of the main study regardless of whether the subject was in main study or the OLE Study. • Included OLE efficacy endpoints. • The dosing and storage instructions for the IP were revised. • Text was revised to indicate that interim analysis was to be performed after 80% to 100% of the subjects had completed 6 months of the treatment. • Administrative changes included addition of OPKO name and logo throughout the document and change in signatories. |
| 03 April 2016 | <p>This amendment was approved internally at OPKO prior to the implementation of all relevant changes and not submitted to regulatory authorities or operationally implemented.</p> |
| 25 April 2016 | <p>The following changes were made to the protocol:</p> <ul style="list-style-type: none"> • The study design was revised to switch all subjects from Cohorts 1 and 2 entering the LT-OLE period (Period IV) to somatrogon 0.66 mg/kg/week. • The OLE Period was split into two periods: OLE (Period III) and LT-OLE (Period IV) until marketing approval in each country. The study visits and assessments for the LT-OLE period were revised. • Text was revised to delete the conduct of interim analysis. • The protocol was amended to clarify that the DSMB was to meet approximately every 6 months or on an ad-hoc basis in case of any safety concerns during the OLE or LT-OLE periods. • The name of Drug Safety contact was updated. • Pregnancy was added under AE as a potential reason for discontinuation from the study. • Administrative changes consisted of minor clarifications, change in General Manager name, corrections of inconsistencies between sections of the protocol, glossary update, choice of words, redundancies deletion, update to Appendices 2 and 3 to reflect changes in study procedures, correction of typographical errors, and logistical clarifications. |

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| 03 October 2017 | <p>The following changes were made to the protocol:</p> <ul style="list-style-type: none"> • The study design was amended to include PEN period (Period V) until marketing approval in their country, subjected to an annual notification to local IEC/IRB of continuation of study, where applicable. Specific criteria for PEN period was added in inclusion/exclusion criteria and efficacy/secondary endpoints were added in the protocol. • Transition from test drug vials to use of the pen was added in this protocol amendment. Instructions for the use of the pen and dose modification were added along with IP maintenance. • This protocol amendment provided clarification for switching to higher dose of 0.66 mg/kg/week. • Information for pregnancy and ECG assessments were included as per regulatory and United States Food and Drug Administration requirements. • Administrative changes included details about transition of the study protocol to Veeva eTMF and change of Sponsor address and staff. Details of vice president of Clinical Development along with details of medical officer were added in the protocol. |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported