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 (± 1368)	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	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hemoglabin Decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Insulin-like growth factor increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Red blood cell count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Thyroxine decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Meniscus cyst			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Clavicle fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	4 / 13 (30.77%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	6	3	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 15 (13.33%)	3 / 14 (21.43%)
occurrences (all)	1	2	4
Iron deficiency anaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Amblyopia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Astigmatism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Eye inflammation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Eyelid oedema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	8	0	0
Hypermetropia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Myopia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	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	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hypothyroidism			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	1 / 14 (7.14%)
occurrences (all)	2	1	1
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Delayed puberty			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Secondary hypogonadism			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Connective tissue disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	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 tonsilities			
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	0 / 13 (0.00%)	2 / 15 (13.33%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Rhinitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Tracheobronchitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Varicella			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Viral infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Corona virus infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rotavirus infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Impaired fasting glucose			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Obesity			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	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	0 / 11 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	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	
Hemoglabin 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	1 / 11 (9.09%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Meniscus cyst			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Clavicle fracture			
subjects affected / exposed	0 / 11 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 11 (9.09%)	4 / 48 (8.33%)	
occurrences (all)	1	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Amblyopia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	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	0 / 11 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Sphincter of Oddi dysfunction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Petechiae			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Hypothyroidism			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	
occurrences (all)	1	4	
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Delayed puberty			

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

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			

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2012	1 Principal Investigator was changed to read Coordinating Investigator 2 Maximum number of participating countries updated 3 Rotation of the injection site updated 4 The Screening period was extended to six weeks 5 The assessment for anti-MOD-4023 Abs removed from Screening 6 Clarify the stratification 7 Assessment of Baseline MOD-4023 (Cohorts 1-3) 8 An HbA1c assessment was added to Visits 4, 11, 12 9 Protocol was amended to remove inclusion criterion number 5 10 The interval between two HT measurements was clarified 11 Karyotype testing was specified to be performed by central laboratory 12 The planned PK/PD analyses were amended 13 Clarify that MOD-4023 was tested in adults in a Phase II 14 The allocation of identification numbers was clarified 16 Assessment of parameters of glucose metabolism in Genotropin patients, at Visits 2 and 4 added 17 Clarify that Lp(a) assessment will be done only at Visit 6 18 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 4 19 Clarify that predicted adult age will be calculated for children above seven years 20 Coordinating Investigator will approval the use of thyroid replacement therapy 21 Clarify that deviations in the weekly dosing during the PK/PD period will be considered as major 22 Clarify that the reporting of SAEs will be done electronically 23 Change in the contact person for SAE reporting 24 Address the possibility of measurement of cortisol levels is a glucagon stimulation test was historically 25 Clarify that both GH-stimulation tests were not required to have been conducted by the central laboratory 26 Clarify that a screening, and not a Baseline adrenocorticotropic hormone (ACTH) test will be done 27 Clarify that a cubital vein will be used for the ACTH test 28 Replace the Wong-Baker image for local pain 29 list the names of the central technical facilities and contractors was amende

26 June 2012	No patients were enrolled at the time this amendment was issued 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	At the time this amendment was issued eight patients had been treated. 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: 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.

23 July 2013	At the time of this amendment 32 patients had been treated. 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 ≤six weeks acceptable for Screening.
01 September 2013	At the time of this amendment, 53 patients had been treated. 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 < ppGH ≤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.

26 January 2015	The following changes were made to the protocol: • 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	This amendment was approved internally at OPKO prior to the implementation of all relevant changes and not submitted to regulatory authorities or operationally implemented.
25 April 2016	The following changes were made to the protocol: • 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.

03 October 2017	The following changes were made to the protocol: • 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported