Clinical trial results:
A Phase 3, Multicenter Study Designed to Evaluate the Efficacy and Safety of a Long Acting hGH Product (MOD-4023) in Adult Subjects with Growth Hormone Deficiency

Summary

EudraCT number	2013-000830-37
Trial protocol	HU SK GR GB AT ES NL PL
Global end of trial date	17 August 2018

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	CP-4-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01909479
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., contact@opko.com
Scientific contact	OPKO Health, Inc., OPKO Health, Inc., 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	17 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2016
Global end of trial reached?	Yes
Global end of trial date	17 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate a clinical superiority of MOD-4023 over placebo in terms of decrease in Trunk Fat Mass (FM) in adult subjects with GHD

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) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study participants.
The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each of the investigational centers participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2013
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	Poland: 23
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Georgia: 4
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Romania: 25
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Ukraine: 18
Country: Number of subjects enrolled	Serbia: 15

Country: Number of subjects enrolled	United States: 34
Worldwide total number of subjects	202
EEA total number of subjects	78

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	195
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 389 subjects were screened for entry into the Main Study and 202 subjects were randomized

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	MOD-4023

Arm description:

Individualized once weekly dose of MOD-4023

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

Dosage and administration details:

Individualized once weekly dose of MOD-4023

Arm title	Placebo

Arm description:

Once weekly administration of placebo

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

Dosage and administration details:

Once weekly administration of placebo

Number of subjects in period 1	MOD-4023	Placebo
Started	135	67
Completed	129	58
Not completed	6	9
Consent withdrawn by subject	3	6

Adverse event, non-fatal	3	2
SIte and study closed by PI	-	1

Period 2	
Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MOD-4023

Arm description:

Individualized once weekly dose of MOD-4023

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

Dosage and administration details:

Individualized once weekly dose of MOD-4023

Arm title	MOD-4023 (Randomized as Placebo)

Arm description:

Individualized once weekly dose of MOD-4023, patient who were initially randomized as Placebo

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

Dosage and administration details:

Individualized once weekly dose of MOD-4023

Number of subjects in period 2[1]	MOD-4023	MOD-4023 (Randomized as Placebo)
Started	128	58
Completed	125	56
Not completed	3	2
Consent withdrawn by subject	2	1

Adverse event, non-fatal	-	1
Lost to follow-up	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: One MOD-4023 subject that completed period 1 withdrew consent and did not continue to period 2

Period 3

Period 3 title	Period 3 LT-OLE
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	MOD-4023

Arm description:

Individualized once weekly dose of MOD-4023

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

Dosage and administration details:

Individualized once weekly dose of MOD-4023

Number of subjects in period 3[2]	MOD-4023
Started	162
Completed	118
Not completed	44
Sponsor's decision	3
Adverse event, serious fatal	1
Personal reasons	3
Consent withdrawn by subject	20
Adverse event, non-fatal	3
Inability to Continue the Study for Any Reason	6
Pregnancy	1
Diabetes not controlled on oral meds and liver tes	1
Evidence of growth of Intracranial Tumor	2

Lost to follow-up	2
Lack of Subject Compliance	1
Occurrence of Malignancy	1

Notes:

[2] - 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: Treatment Period 3, the OLE 52-week period, isn't part of the main study.
A total of 162 subjects signed the informed consent for the LT-OLE study and 161 subjects were treated.

Baseline characteristics

Reporting groups	
Reporting group title	MOD-4023
Reporting group description:	
Individualized once weekly dose of MOD-4023	
Reporting group title	Placebo
Reporting group description:	
Once weekly administration of placebo	

Reporting group values	MOD-4023	Placebo	Total
Number of subjects	135	67	202
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	131	64	195
From 65-84 years	4	3	7
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	58	26	84
Male	77	41	118

End points

End points reporting groups

Reporting group title	MOD-4023
Reporting group description: Individualized once weekly dose of MOD-4023	
Reporting group title	Placebo
Reporting group description: Once weekly administration of placebo	
Reporting group title	MOD-4023
Reporting group description: Individualized once weekly dose of MOD-4023	
Reporting group title	MOD-4023 (Randomized as Placebo)
Reporting group description: Individualized once weekly dose of MOD-4023, patient who were initially randomized as Placebo	
Reporting group title	MOD-4023
Reporting group description: Individualized once weekly dose of MOD-4023	

Primary: Change in Trunk FM, Expressed in Kilograms Measured With DXA, From Baseline to Week 26

End point title	Change in Trunk FM, Expressed in Kilograms Measured With DXA, From Baseline to Week 26
End point description:	
End point type	Primary
End point timeframe: 26 weeks	

End point values	MOD-4023	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	56		
Units: kg				
number (not applicable)	-0.3	0.1		

Statistical analyses

Statistical analysis title	Trunk FM (kg)
Statistical analysis description: Primary Efficacy Analysis: Trunk FM (kg) Change From Baseline in Treatment Period 1 - EP	
Comparison groups	Placebo v MOD-4023

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0821
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.05

Secondary: Change in Total FM, Expressed in Kilograms, Measured With DXA, From Baseline to 26 Weeks

End point title	Change in Total FM, Expressed in Kilograms, Measured With DXA, From Baseline to 26 Weeks

End point description:

End point type	Secondary

End point timeframe:

26 weeks

End point values	MOD-4023	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	56		
Units: kg				
number (not applicable)	-0.18	0.0		

Statistical analyses

Statistical analysis title	Total FM (kg) Change

Statistical analysis description:

Total FM (kg) Change and Percent Change From Baseline in Treatment Period 1 - EP

Comparison groups	MOD-4023 v Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.577
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.55

Secondary: Change in Lean Body Mass, Expressed in Kilograms Measured With DXA, From Baseline to 26

End point title	Change in Lean Body Mass, Expressed in Kilograms Measured With DXA, From Baseline to 26

End point description:

End point type	Secondary

End point timeframe:

26 Weeks

End point values	MOD-4023	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	56		
Units: kg				
number (not applicable)	1.3	0.0		

Statistical analyses

Statistical analysis title	Lean Body Mass Change (kg)

Statistical analysis description:

Lean Body Mass (kg) Change and Percent Change From Baseline in Treatment Period 1 - EP

Comparison groups	Placebo v MOD-4023
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Mixed Model for Repeated Measures (MMRM)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.9

Secondary: Change in Lean Body Mass, Expressed in Kilograms Measured With DXA, From Baseline to 52

End point title	Change in Lean Body Mass, Expressed in Kilograms Measured

	With DXA, From Baseline to 52

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MOD-4023	MOD-4023 (Randomized as Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	55		
Units: kg				
number (not applicable)	1.6	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Trunk FM, Expressed in Kilograms Measured With DXA, From Baseline to 52 Weeks

End point title	Change in Trunk FM, Expressed in Kilograms Measured With DXA, From Baseline to 52 Weeks

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MOD-4023	MOD-4023 (Randomized as Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	55		
Units: kg				
number (not applicable)	-0.2	-0.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of IGF-I and IGF-I SDS levels across study visits in Period I

End point title	Change of IGF-I and IGF-I SDS levels across study visits in

	Period I

End point description:

End point type	Secondary

End point timeframe:

26 weeks

End point values	MOD-4023	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	59		
Units: µg/L				
number (not applicable)	85.6	1.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of IGF-I and IGF-I SDS levels across study visits in Period 2

End point title	Change of IGF-I and IGF-I SDS levels across study visits in Period 2

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MOD-4023	MOD-4023 (Randomized as Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	57		
Units: µg/L				
number (not applicable)	100.6	80.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of IGFBP-3 Levels Across Study Visits in Period 1

End point title	Change of IGFBP-3 Levels Across Study Visits in Period 1

End point description:

End point type	Secondary

End point timeframe:

26 weeks

End point values	MOD-4023	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	59		
Units: µg/L				
number (not applicable)	1266.4	76.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of IGFBP-3 Levels Across Study Visits in Period 2

End point title	Change of IGFBP-3 Levels Across Study Visits in Period 2

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MOD-4023	MOD-4023 (Randomized as Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	57		
Units: µg/L				
number (not applicable)	1618.6	1392.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Achieving Normalization of IGF-1 Levels During and at the End Treatment Period 1 and Period 2

End point title	Proportion of Subjects Achieving Normalization of IGF-1 Levels During and at the End Treatment Period 1 and Period 2

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MOD-4023	Placebo	MOD-4023	MOD-4023 (Randomized as Placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133	65	128	58
Units: Sublects	130	4	127	49

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total FM, Expressed in Kilograms, Measured With DXA, From Baseline to 52 Weeks

End point title	Change in Total FM, Expressed in Kilograms, Measured With DXA, From Baseline to 52 Weeks

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MOD-4023	MOD-4023 (Randomized as Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	55		
Units: kg				
number (not applicable)	-0.06	-0.19		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Trunk FM, Expressed as % Change From Baseline, Measured With DXA, From Baseline to 26 Weeks

End point title	Change in Trunk FM, Expressed as % Change From Baseline, Measured With DXA, From Baseline to 26 Weeks

End point description:

End point type	Secondary
End point timeframe:	
26 weeks	

End point values	MOD-4023	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	56		
Units: kg				
number (not applicable)	-0.9	0.3		

Statistical analyses

Statistical analysis title	Trunk FM as a Percentage of Total FM (kg)
Comparison groups	MOD-4023 v Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Mixed Model for Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	-0.77

Secondary: Change in Trunk FM, Expressed as % Change From Baseline, Measured With DXA, From Baseline to 52 Weeks

End point title	Change in Trunk FM, Expressed as % Change From Baseline, Measured With DXA, From Baseline to 52 Weeks
End point description:	

End point type	Secondary
End point timeframe:	
52 weeks	

End point values	MOD-4023	MOD-4023 (Randomized as Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	55		
Units: kg				
number (not applicable)	-0.9	-0.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were collected throughout the 12 month treatment period 1 and Period 2	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	MOD-4023 Period 1
Reporting group description: -	
Reporting group title	Placebo Period 1
Reporting group description: Once weekly administration of placebo	
Reporting group title	MOD-4023 Period 2
Reporting group description: Treatment Assignments at Period 1	
Reporting group title	Placebo Period 2
Reporting group description: Treatment Assignments at Period 1	
Reporting group title	MOD-4023 Period 3
Reporting group description: LT-OLE- Treatment Assignments at Period 1	
Reporting group title	Placebo Period 3
Reporting group description: LT-OLE - Treatment Assignments at Period 1	

Serious adverse events	MOD-4023 Period 1	Placebo Period 1	MOD-4023 Period 2
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 133 (3.01%)	5 / 65 (7.69%)	5 / 133 (3.76%)
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)			
Haemangioma			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Squamous cell carcinoma of lung			

subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Product issues			
Device loosening			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Joint injury			

subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Pneumothorax traumatic			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Rib fracture			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 133 (0.00%)	1 / 65 (1.54%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 133 (0.00%)	1 / 65 (1.54%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Myocardial infarction			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 133 (0.75%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianopia heteronymous			

subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Spinal claudication			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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			
Abdominal Pain			
subjects affected / exposed	1 / 133 (0.75%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	1 / 65 (1.54%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Disorder			
subjects affected / exposed	1 / 133 (0.75%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Enterocolitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Pituitary-dependent Cushing's syndrom			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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			
Pain in extremity			
subjects affected / exposed	1 / 133 (0.75%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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			
Bronchitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 133 (0.00%)	1 / 65 (1.54%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Respiratory tract infection viral			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 133 (0.00%)	1 / 65 (1.54%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Colonic abscess			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Gastroenteritis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Pneumonia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Pyelonephritis acute			

subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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
Hyponatraemia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (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	Placebo Period 2	MOD-4023 Period 3	Placebo Period 3
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 65 (4.62%)	10 / 111 (9.01%)	8 / 50 (16.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Oedema peripheral			

subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Pyrexia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device loosening			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	1 / 65 (1.54%)	0 / 111 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Atrial Fibrillation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Hemianopia heteronymous			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal claudication			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Gastric Disorder			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Inguinal hernia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 111 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary-dependent Cushing's syndrom			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Synovitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Arthralgia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Diverticulitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Gastroenteritis viral			
subjects affected / exposed	1 / 65 (1.54%)	0 / 111 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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

Urinary Tract Infection			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (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
Appendicitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 111 (0.90%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 65 (1.54%)	0 / 111 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	MOD-4023 Period 1	Placebo Period 1	MOD-4023 Period 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 133 (34.59%)	33 / 65 (50.77%)	28 / 133 (21.05%)
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 133 (8.27%)	5 / 65 (7.69%)	11 / 133 (8.27%)
occurrences (all)	16	5	14
Paraesthesia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	12 / 133 (9.02%)	9 / 65 (13.85%)	4 / 133 (3.01%)
occurrences (all)	32	24	26
Pyrexia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 133 (3.01%)	3 / 65 (4.62%)	0 / 133 (0.00%)
occurrences (all)	4	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 133 (4.51%)	3 / 65 (4.62%)	3 / 133 (2.26%)
occurrences (all)	7	3	4
Pain in extremity			
subjects affected / exposed	2 / 133 (1.50%)	4 / 65 (6.15%)	0 / 133 (0.00%)
occurrences (all)	2	5	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 133 (3.76%)	5 / 65 (7.69%)	10 / 133 (7.52%)
occurrences (all)	5	5	12
Upper respiratory tract infection			

subjects affected / exposed	6 / 133 (4.51%)	4 / 65 (6.15%)	0 / 133 (0.00%)
occurrences (all)	6	6	0
Bronchitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 65 (0.00%)	0 / 133 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo Period 2	MOD-4023 Period 3	Placebo Period 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 65 (24.62%)	56 / 111 (50.45%)	37 / 50 (74.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 65 (3.08%)	7 / 111 (6.31%)	4 / 50 (8.00%)
occurrences (all)	3	10	8
Paraesthesia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	4 / 65 (6.15%)	4 / 111 (3.60%)	4 / 50 (8.00%)
occurrences (all)	17	57	88
Pyrexia			
subjects affected / exposed	0 / 65 (0.00%)	7 / 111 (6.31%)	2 / 50 (4.00%)
occurrences (all)	0	7	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 65 (0.00%)	4 / 111 (3.60%)	3 / 50 (6.00%)
occurrences (all)	0	5	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 65 (9.23%)	3 / 111 (2.70%)	5 / 50 (10.00%)
occurrences (all)	8	3	5
Pain in extremity			

subjects affected / exposed	0 / 65 (0.00%)	0 / 111 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 65 (6.15%)	13 / 111 (11.71%)	5 / 50 (10.00%)
occurrences (all)	5	22	6
Upper respiratory tract infection			
subjects affected / exposed	0 / 65 (0.00%)	10 / 111 (9.01%)	3 / 50 (6.00%)
occurrences (all)	0	12	4
Bronchitis			
subjects affected / exposed	0 / 65 (0.00%)	4 / 111 (3.60%)	3 / 50 (6.00%)
occurrences (all)	0	5	3
Sinusitis			
subjects affected / exposed	0 / 65 (0.00%)	4 / 111 (3.60%)	5 / 50 (10.00%)
occurrences (all)	0	4	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2014	Amendment 1 1. An additional four possible weeks were added to the allowable screening period. 2. Exclusion criteria amended to clarify that ongoing administration of antidiabetic medications/agents would be exclusionary. 3. Exclusion criteria amended to clarify that any diagnosed or ongoing cancer, or history of cancer would be exclusionary. 4. Prolactin levels removed as safety endpoint. 5. A section detailing the use of an unblinded Medical Expert for dose modifications was added.
07 August 2014	Amendment 2 1. Treatment Period 3, the OLE 52-week period was added for the collection of additional safety data. Study conduct amended to include LT-OLE. 2. Specific inclusion and exclusion criteria for Treatment Period 3 added. 3. Additional measures amended to include: a. Change in QoL from baseline across study visits. b. Change in waist to hip ratio from baseline across study visits. c. Change in bone density from baseline on a yearly basis during Treatment Period 3. d. Change in fat and lean body mass from baseline on a yearly basis during Treatment Period 3. e. Change in lipid profile: fasting high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, lipoprotein-a (Lp[a]) from baseline on a six months basis. 4. Clarification that Treatment Period 3 will continue until market approval in each country. 5. A secondary study objective was added: To monitor long-term safety and efficacy of somatrogon in adult subjects with GHD who completed Treatment Periods 1 and 2 of this study. 6. Treatment Period 2 and Treatment period 3 revised to clarify that no placebo group would be included. 7. Text added to indicate that during Treatment Period 3 Investigators would receive IGF-1 levels and make dose adjustments as needed.

04 July 2016	Amendment 3 1. A washout period of two to eight weeks was specified between Treatment Periods 2 and 3 and the signing of a Treatment Period 3 informed consent form (ICF) was described. 2. The assessment of adrenal function was added as a requirement for Treatment Period 2. 3. During the first year of Treatment Period 3 antibodies (Abs) would be assessed on dosing day, prior to dosing, and from the second year of Treatment Period 3 it would be done during regular clinic visits. 4. In the first year of Treatment Period 3, at Visit 20, the ECG assessment must be performed seven to 15 hours post dosing to assess cardiac activity at the time to maximum concentration. 5. Inclusion criteria for Treatment Period 3 was amended to clarify that subjects must have completed Treatment Periods 1 and 2 with adequate compliance 6. The exclusion criterion for Treatment Period 3 of > three months duration since the last dose of somatrogon could be waived by the Medical Monitor following evaluation of the subject. 7. Detectable NAb was removed as an exclusion to Treatment Period 3. 8. During Treatment Period 3, the IRT system would propose dose modifications to the Investigator, however the ultimate decision for dose modification would be the responsibility of the Investigator. 9. Thyroid and adrenal function would be performed at Visit 6 and Visit 10. 10. The primary EP was to consist of all intent-to-treat (ITT) subjects who received at least one dose of study treatment and had at least one post randomization measurement of trunk FM at Week 15 or Week 26.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported