Clinical trial results:
EFFICACY AND SAFETY OF ORAL OCTREOLIN™ IN PATIENTS WITH ACROMEGALY WHO ARE CURRENTLY RECEIVING PARENTERAL SOMATOSTATIN ANALOGS

Summary

EudraCT number	2011-002912-10
Trial protocol	HU NL GB DE SK PL IT SI LT
Global end of trial date	30 May 2014

Results information

Result version number	v1 (current)
This version publication date	30 July 2017
First version publication date	30 July 2017

Trial information

Trial identification

Sponsor protocol code	CH-ACM-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01412424
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiasma, Inc.
Sponsor organisation address	831 Beacon Street, Suite no. 313, Newton Centre, Massachusetts, United States, 02459
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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	30 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 May 2014
Global end of trial reached?	Yes
Global end of trial date	30 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of Octreolin therapy on Insulin-like Growth Factor 1 (IGF-1) levels and Growth Hormone (GH) levels as measures of response

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 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	Netherlands: 17
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Slovenia: 4
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Serbia: 13
Worldwide total number of subjects	155
EEA total number of subjects	109

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	127
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study comprised a Core Treatment Period (consisting of a Dose Escalation Phase and a Fixed Dose Phase) followed by a voluntary Extension Period. The optimum dose identified for each patient during the Dose Escalation Phase was maintained in the Fixed Dose Phase and the Extension Period.

Pre-assignment

Screening details:

At least 150 adult patients who were diagnosed with acromegaly and who, at screening, were receiving regular parenteral therapy at a stable dose of an SRL for at least 3 months, and who were responders, were to be enrolled.

Period 1

Period 1 title	Core Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Octreotide capsules

Arm description:

All patients

Arm type	Experimental
Investigational medicinal product name	Octreotide 20 mg capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral octreotide treatment was started at a dose of 40 mg/day (20 mg bid). Dose escalation was based on measurement of the patient's IGF-1 levels and acromegaly-related symptoms. The dose was titrated on an individual basis, stepwise from 40 mg/day to 60 mg/day (40 mg in the morning, 20 mg in the evening) to a maximum of 80 mg/day (40 mg bid) until maximum hormonal suppression was achieved.

Number of subjects in period 1	Octreotide capsules
Started	155
Completed	102
Not completed	53
Consent withdrawn by subject	5
Treatment failure	24
Sponsor request	1
Adverse event	21
Lost to follow-up	2

Period 2

Period 2 title	Extension Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Octreotide capsules

Arm description:

All patients

Arm type	Experimental
Investigational medicinal product name	Octreotide 20 mg capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral octreotide treatment was started at a dose of 40 mg/day (20 mg bid). Dose escalation was based on measurement of the patient's IGF-1 levels and acromegaly-related symptoms. The dose was titrated on an individual basis, stepwise from 40 mg/day to 60 mg/day (40 mg in the morning, 20 mg in the evening) to a maximum of 80 mg/day (40 mg bid) until maximum hormonal suppression was achieved.

Number of subjects in period 2[1]	Octreotide capsules
Started	88
Completed	82
Not completed	6
Consent withdrawn by subject	2
Treatment failure	2
Adverse event	2

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: ontinuation of treatment in the 6-month extension period was voluntary. Patients completing the Core Treatment Period might have chosen to not continue treatment in the extension period and might have discontinued the study. Therefore, the number of patients completing the Core Treatment Period is higher than the number of patients starting the Extension Treatment Period.

Baseline characteristics

Reporting groups

Reporting group title	Core Treatment Period

Reporting group description: -

Reporting group values	Core Treatment Period	Total	
Number of subjects	155	155	
Age categorical Units: Subjects			
Adults (18-64 years)	127	127	
From 65-84 years	28	28	
Age continuous Units: years			
arithmetic mean	54.2		
standard deviation	± 11.5	-	
Gender categorical Units: Subjects			
Female	67	67	
Male	88	88	

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients enrolled who had received any amount of study drug and had at least one post-baseline assessment

Subject analysis set title	Modified intention-to-treat population
Subject analysis set type	Full analysis

Subject analysis set description:

All enrolled patients who received any amount of study drug and had at least one post-baseline assessment of insulin-like growth factor 1 (IGF-1) or growth hormone (GH)

Subject analysis set title	Extension intention-to-treat population
Subject analysis set type	Full analysis

Subject analysis set description:

All patients enrolled in the Extension Treatment Period

Subject analysis set title	Fixed dose population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Enrolled patients who received any amount of study drug, had at least one post-baseline IGF-1 or GH assessment, and had entered the Fixed Dose Phase of the Core Treatment Period

Reporting group values	Safety population	Modified intention-to-treat population	Extension intention-to-treat population
Number of subjects	155	151	88
Age categorical Units: Subjects			
Adults (18-64 years)	127		
From 65-84 years	28		

Age continuous Units: years arithmetic mean standard deviation	 54.2 ± 11.5	 ±	 ±
Gender categorical Units: Subjects			
Female Male	67 88		

Reporting group values	Fixed dose population		
Number of subjects	110		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years arithmetic mean standard deviation	 ±	 	
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Octreotide capsules
Reporting group description:	
All patients	
Reporting group title	Octreotide capsules
Reporting group description:	
All patients	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients enrolled who had received any amount of study drug and had at least one post-baseline assessment	
Subject analysis set title	Modified intention-to-treat population
Subject analysis set type	Full analysis
Subject analysis set description:	
All enrolled patients who received any amount of study drug and had at least one post-baseline assessment of insulin-like growth factor 1 (IGF-1) or growth hormone (GH)	
Subject analysis set title	Extension intention-to-treat population
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients enrolled in the Extension Treatment Period	
Subject analysis set title	Fixed dose population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Enrolled patients who received any amount of study drug, had at least one post-baseline IGF-1 or GH assessment, and had entered the Fixed Dose Phase of the Core Treatment Period	

Primary: Percentage of responders at the end of the Core Treatment Period

End point title	Percentage of responders at the end of the Core Treatment Period[1]
End point description:	
A responder was defined as patient with a serum IGF-1 concentration of <1.3 times the upper limit of normal (ULN) (adjusted for age and gender) and a GH concentration <2.5 ng/mL. The GH concentration was the mean of 5 fasted GH serum concentrations collected at 30-minute intervals for 2 h, 2 to 4 h after octreotide administration. The IGF-1 concentration was determined in serum samples taken at the same visits GH concentration was assessed.	
End point type	Primary
End point timeframe:	
End of the Core Treatment Period (up to 7 months)	

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: This primary endpoint was analysed using descriptive statistics only. No inferential testing was applied. A p-value was not defined.

End point values	Octreotide capsules	Modified intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	151	151		
Units: percent				

number (confidence interval 95%)	64.9 (58.4 to 74.2)	64.9 (58.4 to 74.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of responders at the end of the Extension Treatment Period

End point title	Percentage of responders at the end of the Extension Treatment Period[2]

End point description:

A responder was defined as patient with a serum IGF-1 concentration of <1.3 times the ULN (adjusted for age and gender) and a GH concentration <2.5 ng/mL. The GH concentration was the mean of 5 fasted GH serum concentrations collected at 30-minute intervals for 2 h, 2 to 4 h after octreotide administration. The IGF-1 concentration was determined in serum samples taken at the same visits GH concentration was assessed.

End point type	Primary

End point timeframe:

End of the Extension Treatment Period (up to 13 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This primary endpoint was analysed using descriptive statistics only. No inferential testing was applied. A p-value was not defined.

End point values	Octreotide capsules	Extension intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	88	88		
Units: percent				
arithmetic mean (confidence interval 98%)	78.4 (68.4 to 86.5)	78.4 (68.4 to 86.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with specified IGF-1 and GH concentrations at baseline and at the end of the Core Treatment Period

End point title	Percentage of patients with specified IGF-1 and GH concentrations at baseline and at the end of the Core Treatment Period

End point description:

Percentage of patients with the following serum IGF-1 and GH concentrations at baseline (BL) and at the end of the Core Treatment Period (CTP): IGF-1 <1.3 x ULN and GH <5.0 ng/mL; IGF-1 <1.3 x ULN and GH <1.0 ng/mL, IGF-1 ≤1 x ULN and GH < 5.0 ng/mL, IGF-1 ≤1 x ULN and GH <2.5 ng/mL, IGF-1 ≤1 x ULN and GH <1.0 ng/mL, IGF-1 <1.3 x ULN, IGF-1 ≤1 x ULN, GH <5.0 ng/mL, GH <2.5 ng/mL, GH <1.0 ng/mL, IGF-1 ≥1.3 x ULN and GH <2.5 ng/mL, IGF-1 <1.3 x ULN and GH ≥2.5 ng/mL, and IGF-1 ≥1.3 x ULN and GH ≥2.5 ng/mL.

The GH concentration was the mean of 5 fasted GH serum concentrations collected at 30 minute intervals for 2 h, 2 to 4 h after octreotide administration. IGF-1 concentration was determined in serum samples taken at the same visits GH concentration was assessed.

End point type	Secondary

End point timeframe:

Baseline (BL) and end of the Core Treatment Period (CTP): up to 7 months

End point values	Octreotide capsules			
Subject group type	Reporting group			
Number of subjects analysed	151			
Units: percent				
number (not applicable)				
IGF-1 <1.3 x ULN and GH <5 ng/mL: BL	91.4			
IGF-1 <1.3 x ULN and GH <5 ng/mL: CTP	65.6			
IGF-1 <1.3 x ULN and GH <1 ng/mL: BL	62.9			
IGF-1 <1.3 x ULN and GH <1 ng/mL: CTP	53			
IGF-1 ≤1 x ULN and GH <5 ng/mL: BL	63.6			
IGF-1 ≤1 x ULN and GH <5 ng/mL: CTP	35.8			
IGF-1 ≤1 x ULN and GH <2.5 ng/mL: BL	61.6			
IGF-1 ≤1 x ULN and GH <2.5 ng/mL: CTP	35.8			
IGF-1 ≤1 x ULN and GH <1 ng/mL: BL	43			
IGF-1 ≤1 x ULN and GH <1 ng/mL: CTP	31.8			
IGF-1 <1.3 x ULN: BL	91.4			
IGF-1 <1.3 x ULN: CTP	66.9			
IGF-1 ≤1 x ULN: BL	63.6			
IGF-1 ≤1 x ULN: CTP	37.1			
GH <5 ng/mL: BL	100			
GH <5 ng/mL: CTP	97.4			
GH <2.5 ng/mL: BL	96			
GH <2.5 ng/mL: CTP	94.7			
GH <1 ng/mL: BL	66.2			
GH <1 ng/mL: CTP	77.5			
IGF-1 ≥1.3 x ULN and GH <2.5 ng/mL: BL	7.3			
IGF-1 ≥1.3 x ULN and GH <2.5 ng/mL: CTP	29.8			
IGF-1 <1.3 x ULN and GH ≥2.5 ng/mL: BL	2.6			
IGF-1 <1.3 x ULN and GH ≥2.5 ng/mL: CTP	0.7			
IGF-1 ≥1.3 x ULN and GH ≥2.5 ng/mL: BL	1.3			
IGF-1 ≥1.3 x ULN and GH ≥2.5 ng/mL: CTP	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance of response during the Fixed Dose Phase of the Core Treatment Period

End point title	Maintenance of response during the Fixed Dose Phase of the Core Treatment Period

End point description:

Maintenance of response during the Fixed Dose Phase (FDP) of the Core Treatment Period (CTP) was defined as the percentage of patients with an IGF-1 concentration <1.3 x ULN at the beginning of the Fixed Dose Phase of the Core Treatment Period and at the end of the Core Treatment Period. IGF-1 concentration was determined in serum samples taken at the same visits the GH concentration was assessed.

End point type	Secondary

End point timeframe:

Beginning of the Fixed Dose Phase (FDP) of the Core Treatment Period (CTP) and end of the Core Treatment Period (CTP): up to 7 months

End point values	Octreotide capsules			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: percent				
number (not applicable)				
Beginning of the FDP of the CTP	82.7			
End of the CTP	80			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with specified IGF-1 and GH concentrations at baseline and at the end of the Extension Treatment Period

End point title	Percentage of patients with specified IGF-1 and GH concentrations at baseline and at the end of the Extension Treatment Period

End point description:

Percentage of patients with the following serum IGF-1 and GH concentrations at beginning (BETP) and at the end of the Extension Treatment Period (EETP): IGF-1 <1.3 x ULN and GH <5.0 ng/mL; IGF-1 <1.3 x ULN and GH <1.0 ng/mL, IGF-1 ≤1 x ULN and GH < 5.0 ng/mL, IGF-1 ≤1 x ULN and GH <2.5 ng/mL, IGF-1 ≤1 x ULN and GH <1.0 ng/mL, IGF-1 <1.3 x ULN, IGF-1 ≤1 x ULN, GH <5.0 ng/mL, GH <2.5 ng/mL, GH <1.0 ng/mL, IGF-1 ≥1.3 x ULN and GH <2.5 ng/mL, IGF-1 <1.3 x ULN and GH ≥2.5 ng/mL, and IGF-1 ≥1.3 x ULN and GH ≥2.5 ng/mL.
The GH concentration was the mean of 5 fasted GH serum concentrations collected at 30 minute intervals for 2 h,
2 to 4 h after octreotide administration. IGF-1 concentration was determined in serum samples taken at the same visits GH concentration was assessed.

End point type	Secondary

End point timeframe:

Baseline and end of the Extension Treatment Period (up to 6 months)

End point values	Octreotide capsules			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: percent				
number (not applicable)				
IGF-1 <1.3 x ULN and GH <5 ng/mL: BETP	84.1			
IGF-1 <1.3 x ULN and GH <5 ng/mL: EETP	79.5			
IGF-1 <1.3 x ULN and GH <1 ng/mL: BETP	69.3			
IGF-1 <1.3 x ULN and GH <1 ng/mL: EETP	68.2			
IGF-1 ≤1 x ULN and GH <5 ng/mL: BETP	48.9			
IGF-1 ≤1 x ULN and GH <5 ng/mL: EETP	50			
IGF-1 ≤1 x ULN and GH <2.5 ng/mL: BETP	48.9			
IGF-1 ≤1 x ULN and GH <2.5 ng/mL: EETP	50			
IGF-1 ≤1 x ULN and GH <1 ng/mL: BETP	42			
IGF-1 ≤1 x ULN and GH <1 ng/mL: EETP	44.3			
IGF-1 <1.3 x ULN: BETP	84.1			
IGF-1 <1.3 x ULN: EETP	79.5			
IGF-1 ≤1 x ULN: BETP	48.9			
IGF-1 ≤1 x ULN: EETP	50			
GH <5 ng/mL: BETP	100			
GH <5 ng/mL: EETP	97.7			
GH <2.5 ng/mL: BETP	98.9			
GH <2.5 ng/mL: EETP	95.5			
GH <1 ng/mL: BETP	83			
GH <1 ng/mL: EETP	83			
IGF-1 ≥1.3 x ULN and GH <2.5 ng/mL: BETP	14.8			
IGF-1 ≥1.3 x ULN and GH <2.5 ng/mL: EETP	17			
IGF-1 <1.3 x ULN and GH ≥2.5 ng/mL: BETP	0			
IGF-1 <1.3 x ULN and GH ≥2.5 ng/mL: EETP	1.1			
IGF-1 ≥1.3 x ULN and GH ≥2.5 ng/mL: BETP	1.1			
IGF-1 ≥1.3 x ULN and GH ≥2.5 ng/mL: EETP	3.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance of response during the Extension Treatment Period

End point title	Maintenance of response during the Extension Treatment Period

End point description:

Maintenance of an IGF-1 response during the Extension Treatment Period was defined as the percentage of patients with IGF-1 concentration <1.3 x ULN at the beginning of the Extension Treatment Period and at the end of the Extension Treatment Period. IGF-1 concentration was determined in serum samples taken at the same visits GH concentration was assessed.

End point type	Secondary

End point timeframe:

Beginning of the Extension Treatment Period and end of the Extension Treatment Period (up to 13 months)

End point values	Octreotide capsules			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: percent				
arithmetic mean (confidence interval 95%)				
Beginning of the FDP of the CTP	87.8 (78.2 to 94.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with improved or maintained acromegaly symptoms at the end of the Extension Treatment Period

End point title	Percentage of patients with improved or maintained acromegaly symptoms at the end of the Extension Treatment Period

End point description:

The severity (absent, mild, moderate, severe) of the 5 acromegaly symptoms headache, perspiration, asthenia, swelling of extremities, and joint pain was assessed at baseline and at the end of the Extension Treatment Period. The percentage of patients with improved or maintained (no change) acromegaly symptoms from baseline to the end of the Extension Treatment Period is reported.

End point type	Secondary

End point timeframe:

Baseline and end of the Extension Treatment Period (up to 13 months)

End point values	Octreotide capsules			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: percent				
arithmetic mean (confidence interval 95%)				
Maintained	27 (18.3 to 37.8)			
Improved	57 (45.8 to 67.3)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of patients with ≥1, 2, or 3 acromegaly symptoms at baseline and at the end of the Extension Treatment Period (EETP)

End point title	Percentage of patients with ≥1, 2, or 3 acromegaly symptoms at baseline and at the end of the Extension Treatment Period (EETP)

End point description:

Percentage of patients who had ≥1, 2, or 3 of the 5 acromegaly symptoms (headaches, perspiration, asthenia, swelling of extremities, joint pain) of any severity (mild, moderate, severe). This was a post hoc analysis.

End point type	Post-hoc

End point timeframe:

Baseline and end of the Extension Treatment Period (up to 13 months)

End point values	Octreotide capsules			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: percent				
number (not applicable)				
1 symptom, baseline	78			
1 symptom, EETP	65			
2 symptoms, baseline	61			
2 symptoms, EETP	43			
3 symptoms, baseline	43			
3 symptoms, EETP	25			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Core Treatment Period plus Extension Treatment Period (up to 13 months)	
Adverse event reporting additional description:	
The total number of patients with AEs is greater than the 155 patients enrolled in the study because of the study's dose-escalation design: patients might have experienced AEs at more than one dose level they received during the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14

Reporting groups	
Reporting group title	Octreotide 40 mg
Reporting group description:	
Patients receiving octreotide 40 mg/day (20 mg/bid) for up to 13 months	
Reporting group title	Octreotide 60 mg
Reporting group description:	
Patients receiving octreotide 60 mg/day (40 mg in the morning and 20 mg in the evening) for up to 13 months	
Reporting group title	Octreotide 80 mg
Reporting group description:	
Patients receiving octreotide 80 mg/day (40 mg/bid) for up to 13 months	

Serious adverse events	Octreotide 40 mg	Octreotide 60 mg	Octreotide 80 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 155 (5.81%)	7 / 91 (7.69%)	8 / 58 (13.79%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	0 / 155 (0.00%)	1 / 91 (1.10%)	0 / 58 (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
Colon cancer			
subjects affected / exposed	0 / 155 (0.00%)	1 / 91 (1.10%)	0 / 58 (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
Meningioma			

subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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
Pancreatic neoplasm			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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
Pyrexia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Investigations			
Transaminases increased			

subjects affected / exposed	0 / 155 (0.00%)	1 / 91 (1.10%)	0 / 58 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bradycardia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 155 (1.29%)	0 / 91 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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
Syncope			
subjects affected / exposed	0 / 155 (0.00%)	1 / 91 (1.10%)	0 / 58 (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
Transient ischaemic attack			

subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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
Blood and lymphatic system disorders			
Spleen disorder			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 91 (1.10%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Bile duct stone			

subjects affected / exposed	0 / 155 (0.00%)	1 / 91 (1.10%)	0 / 58 (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
Cholecystitis acute			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 155 (0.00%)	1 / 91 (1.10%)	0 / 58 (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			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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
Polymyalgia rheumatica			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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
Corneal abscess			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (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

Herpes simplex ophthalmic			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 91 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 91 (1.10%)	0 / 58 (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
Hyponatraemia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 91 (0.00%)	1 / 58 (1.72%)
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	Octreotide 40 mg	Octreotide 60 mg	Octreotide 80 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 155 (66.45%)	51 / 91 (56.04%)	31 / 58 (53.45%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 155 (3.87%)	4 / 91 (4.40%)	3 / 58 (5.17%)
occurrences (all)	8	4	4
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 155 (28.39%)	18 / 91 (19.78%)	20 / 58 (34.48%)
occurrences (all)	46	38	64

Dizziness			
subjects affected / exposed	8 / 155 (5.16%)	1 / 91 (1.10%)	2 / 58 (3.45%)
occurrences (all)	9	1	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	27 / 155 (17.42%)	11 / 91 (12.09%)	8 / 58 (13.79%)
occurrences (all)	40	17	11
Oedema peripheral			
subjects affected / exposed	19 / 155 (12.26%)	8 / 91 (8.79%)	5 / 58 (8.62%)
occurrences (all)	31	10	5
Fatigue			
subjects affected / exposed	6 / 155 (3.87%)	1 / 91 (1.10%)	2 / 58 (3.45%)
occurrences (all)	8	1	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	30 / 155 (19.35%)	14 / 91 (15.38%)	6 / 58 (10.34%)
occurrences (all)	35	16	10
Diarrhoea			
subjects affected / exposed	18 / 155 (11.61%)	11 / 91 (12.09%)	4 / 58 (6.90%)
occurrences (all)	22	15	5
Dyspepsia			
subjects affected / exposed	11 / 155 (7.10%)	2 / 91 (2.20%)	1 / 58 (1.72%)
occurrences (all)	15	2	1
Abdominal pain upper			
subjects affected / exposed	10 / 155 (6.45%)	2 / 91 (2.20%)	3 / 58 (5.17%)
occurrences (all)	11	3	3
Flatulence			
subjects affected / exposed	10 / 155 (6.45%)	1 / 91 (1.10%)	2 / 58 (3.45%)
occurrences (all)	10	2	3
Abdominal pain			
subjects affected / exposed	5 / 155 (3.23%)	7 / 91 (7.69%)	1 / 58 (1.72%)
occurrences (all)	5	8	1
Abdominal distension			
subjects affected / exposed	7 / 155 (4.52%)	4 / 91 (4.40%)	1 / 58 (1.72%)
occurrences (all)	8	5	1
Vomiting			

subjects affected / exposed	4 / 155 (2.58%)	3 / 91 (3.30%)	4 / 58 (6.90%)
occurrences (all)	4	3	4
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	4 / 155 (2.58%)	3 / 91 (3.30%)	3 / 58 (5.17%)
occurrences (all)	4	3	3
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	23 / 155 (14.84%)	9 / 91 (9.89%)	6 / 58 (10.34%)
occurrences (all)	44	17	7
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	25 / 155 (16.13%)	20 / 91 (21.98%)	11 / 58 (18.97%)
occurrences (all)	48	28	21
Myalgia			
subjects affected / exposed	2 / 155 (1.29%)	2 / 91 (2.20%)	3 / 58 (5.17%)
occurrences (all)	2	2	3
Neck pain			
subjects affected / exposed	3 / 155 (1.94%)	1 / 91 (1.10%)	3 / 58 (5.17%)
occurrences (all)	3	1	6
Back pain			
subjects affected / exposed	5 / 155 (3.23%)	3 / 91 (3.30%)	1 / 58 (1.72%)
occurrences (all)	7	3	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 155 (3.23%)	4 / 91 (4.40%)	5 / 58 (8.62%)
occurrences (all)	10	4	6
Influenza			
subjects affected / exposed	6 / 155 (3.87%)	4 / 91 (4.40%)	3 / 58 (5.17%)
occurrences (all)	6	4	4
Upper respiratory tract infection			
subjects affected / exposed	6 / 155 (3.87%)	2 / 91 (2.20%)	3 / 58 (5.17%)
occurrences (all)	6	2	4
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed occurrences (all)	3 / 155 (1.94%) 3	2 / 91 (2.20%) 2	3 / 58 (5.17%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2011	Amendment 1 specified pituitary MRI versus brain MRI; clarified the patient inclusion age range of 18 to 75 years; added assessments of anti-octreotide antibodies, and safety assessments of insulin, TSH, free T4, vitamin B12, and HbA1c; modified a secondary efficacy endpoint by adding an analysis of the proportion of patients with a mean GH concentration of <1.0 ng/mL; added a new secondary efficacy endpoint of proportion of patients with both normalized IGF-1 levels (adjusted for age) and mean integrated GH over 2 h <2.5 ng/mL; clarified dose escalation; clarified use of prohibited concomitant medications; and clarified the Schedule of Activities table by including more Information.
22 May 2012	Amendment 2 added a 6-month Extension Treatment Period as an option to eligible patients and specified eligibility criteria; allowed for rescreening of patients; clarified the timing of study visits so that the Dose Escalation Phase and the Fixed Dose Phase of the Core Treatment Period had a total duration of at least 7 months; specified that the primary efficacy endpoint and analysis pertained to the Core Treatment Period; specified that there were 2 separate analyses for the Core Treatment Period and the Extension Treatment Period; clarified that serum pregnancy tests were performed at all study visits; added microscopic observations to the screening urinalysis; revised the octreotide antibody sampling time points to allow for the evaluation of the effect of octreotide antibodies on the PK profile of MYCAPSSA; added an exploratory efficacy endpoint for MYCAPSSA PK; added an exploratory efficacy endpoint for octreotide antibodies; clarified study visit procedures to be performed in the event of early discontinuation; specified a visit window for the Follow-Up Period and revised study procedures at the Follow-Up visit; added 5 supplemental questions to the TSQM; and revised the Schedule of Activities to include the 6-month Extension Treatment Period and modified the table footnotes accordingly.
07 December 2012	Amendment 3 permitted the use of serum GH samples that were stored after analysis to complete a full set of visit TA1, TA2, TA4, and TB6/EOT octreotide antibody sample analysis for each patient completing the study; added the inclusion of octreotide antibody analysis at time points TA1, TA2, TA4 and TB6/EOT; allowed stored serum GH samples to be used for octreotide PK analysis for the PK sub-study; and introduced a correction to the timing of diary card completion.
06 December 2013	Amendment 4 included modifications to study endpoints and response categories to allow more educated and informative data interpretation; added the Food Intake and Oral Octreolin Administration Questionnaire as a study procedure to assess the timing of dose administration and relation to food and beverage consumption; and introduced updates to the contact information for the sponsor and CROs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported