



Clinical trial results:

Extension to a multicenter, randomized, crossover, open label, dose finding study to compare the safety, efficacy and PK/PD relationship of multiple doses of SOM230 (200, 400 and 600 µg b.i.d.) and doses of open label Sandostatin (100 µg t.i.d.) in acromegalic patients

Summary

EudraCT number	2004-002849-12
Trial protocol	GB IT ES
Global end of trial date	06 December 2013

Results information

Result version number	v1
This version publication date	13 July 2016
First version publication date	13 August 2015

Trial information

Trial identification

Sponsor protocol code	CSOM230B2201E1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00171730
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002 , Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 /
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 /

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	06 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and efficacy of SOM230 in patients with acromegaly

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	30
EEA total number of subjects	17

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)	27
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This extension study was an open label, single arm, multi-center study inpatients with acromegaly who had completed all four treatment regimens in the core study and achieved biochemical control or had clinically relevant improvement according to Investigator judgment, from at least one of the pasireotide regimens.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Pasireotide s.c. overall
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Arm description:

Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg).

Arm type	Experimental
Investigational medicinal product name	pasireotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg).

Number of subjects in period 1	Pasireotide s.c. overall
Started	30
Completed	15
Not completed	15
Consent withdrawn by subject	3
Adverse event, non-fatal	3
'Unsatisfactory therapeutic effect '	8
'Abnormal laboratory value(s) '	1

Baseline characteristics

Reporting groups

Reporting group title	Pasireotide s.c. overall
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Reporting group description:

Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg).

Reporting group values	Pasireotide s.c. overall	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Adults (18-64 years)	27	27	
From 65-84 years	3	3	
Age continuous Units: years			
arithmetic mean	45.1		
standard deviation	± 15.48	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	14	14	

Subject analysis sets

Subject analysis set title	Pasireotide s.c. <1200 µg/d
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg). <1200 µg/day (n=30)

Subject analysis set title	Pasireotide s.c. 1200 to <1500 µg/d
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg). 1200 to <1500 µg/day (n=30)

Subject analysis set title	Pasireotide s.c. ≥1500 µg/d
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg). ≥ 1500 µg/day (n=12)

Reporting group values	Pasireotide s.c. <1200 µg/d	Pasireotide s.c. 1200 to <1500 µg/d	Pasireotide s.c. ≥1500 µg/d
Number of subjects	30	30	11
Age categorical Units: Subjects			
Adults (18-64 years)	27	27	11
From 65-84 years	3	3	0

Age continuous			
Units: years			
arithmetic mean	45.1	45.1	42.8
standard deviation	± 15.48	± 15.48	± 12.29
Gender categorical			
Units: Subjects			
Female	16	16	8
Male	14	14	3

End points

End points reporting groups

Reporting group title	Pasireotide s.c. overall
Reporting group description:	
Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg).	
Subject analysis set title	Pasireotide s.c. <1200 µg/d
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg). <1200 µg/day (n=30)	
Subject analysis set title	Pasireotide s.c. 1200 to <1500 µg/d
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg). 1200 to <1500 µg/day (n=30)	
Subject analysis set title	Pasireotide s.c. ≥1500 µg/d
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients received pasireotide as a daily s.c. injection every 12 hours at 9:00 AM and 9:00 PM at the dose at which the biochemical control was achieved (either 200, 400, or 600 µg). ≥ 1500 µg/day (n=12)	

Primary: Growth hormone and IGF-1 observed response rates by dose class

End point title	Growth hormone and IGF-1 observed response rates by dose class ^[1]
End point description:	
A patient was a responder to a dose level if the mean GH level after dosing (t30, t60, t90, and t120) was below/equal to 2.5µg/L, and if the mean of IGF-1 of the two predose values (t-30, t-1) was within normal limits for age-sex matched controls. If three or more of t30, t60, t90, or t120 were missing, mean GH was considered missing. If either t-30 or t-1 was missing, mean IGF-1 was considered missing.	
End point type	Primary
End point timeframe:	
Month 3, 6 and 9	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analyses have been specified for this primary end point.

End point values	Pasireotide s.c. overall	Pasireotide s.c. <1200 µg/d	Pasireotide s.c. 1200 to <1500 µg/d	Pasireotide s.c. ≥1500 µg/d
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30 ^[2]	30 ^[3]	30 ^[4]	11 ^[5]
Units: percentage of responders				
number (not applicable)				
Month 3	25	17.6	36.4	0
Month 6	35.7	80	30	0
Month 9	23.1	20	28.6	14.3

Notes:

[2] - n = 7, 10, 6

[3] - n = 3, 4, 1

[4] - n = 4, 6, 4

[5] - n = -, 0, 1

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor response

End point title	Time to tumor response
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End point description:

Tumor response was defined as at least 20% decrease in tumor volume from baseline.

End point type	Secondary
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End point timeframe:

baseline to at least a 20% decrease in pituitary tumor volume

End point values	Pasireotide s.c. overall			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: months				
median (inter-quartile range (Q1-Q3))	12.2 (4.9 to 19.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary MRI pituitary tumor volumes

End point title	Summary MRI pituitary tumor volumes
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End point description:

End point type	Secondary
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End point timeframe:

Core study baseline till the last assessment of the extension study

End point values	Pasireotide s.c. overall			
Subject group type	Reporting group			
Number of subjects analysed	30 ^[6]			
Units: cubic mm				
arithmetic mean (standard deviation)				
Core study baseline	4457.4 (± 4891.98)			
Month 9	2839.3 (± 2710.61)			
Month 27	2536 (± 2219.13)			
Month 63	456 (± 381.84)			
Month 75	1016 (± 872.39)			
Month 99	180 (± 0)			

Notes:

[6] - n = 29, 16, 5, 2, 3, 1

Statistical analyses

No statistical analyses for this end point

Secondary: Symptoms of acromegaly

End point title	Symptoms of acromegaly
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End point description:

Participants scored the following symptoms of acromegaly: Headache, perspiration, paresthesia, fatigue, osteoarthritis, and carpal tunnel syndrome on a 5-point scale (0 = None/absent, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe).

End point type	Secondary
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End point timeframe:

Core study baseline till the last assessment of the extension study

End point values	Pasireotide s.c. overall			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of participants				
number (not applicable)				
Headache - 0	46.7			
Headache - 1	26.7			
Headache - 2	6.7			
Headache - 3	0			
Headache - 4	0			
Headache - Not done	20			
Perspiration - 0	20			
Perspiration - 1	33.3			
Perspiration - 2	23.3			
Perspiration - 3	3.3			
Perspiration - 4	0			

Perspiration - Not done	20			
Paresthesiae - 0	50			
Paresthesiae - 1	16.7			
Paresthesiae - 2	13.3			
Paresthesiae - 3	0			
Paresthesiae - 4	0			
Paresthesiae - Not done	20			
Fatigue - 0	26.7			
Fatigue - 1	26.7			
Fatigue - 2	13.3			
Fatigue - 3	13.3			
Fatigue - 4	0			
Fatigue - Not done	20			
Osteoarthralgia - 0	40			
Osteoarthralgia - 1	23.3			
Osteoarthralgia - 2	10			
Osteoarthralgia - 3	3.3			
Osteoarthralgia - 4	3.3			
Osteoarthralgia - Not done	20			
Carpal tunnel syndrome - 0	56.7			
Carpal tunnel syndrome - 1	10			
Carpal tunnel syndrome - 2	10			
Carpal tunnel syndrome - 3	3.3			
Carpal tunnel syndrome - 4	0			
Carpal tunnel syndrome - Not done	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Epworth Sleepiness Scale by situation (Epworth sleepiness scale)

End point title	Summary of Epworth Sleepiness Scale by situation (Epworth sleepiness scale)
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End point description:

Sleep apnea symptoms were assessed using the Epworth Sleepiness Scale were in the categories 0 = Would never doze, 1 = Slight chance of dozing, 2 = Moderate chance of dozing, 3 = High chance of dozing.

End point type	Secondary
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End point timeframe:

Core study baseline till the last assessment of the extension study

End point values	Pasireotide s.c. overall			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of participants				
number (not applicable)				
Sitting and reading - 0	36.7			
Sitting and reading - 1	23.3			
Sitting and reading - 2	23.3			
Sitting and reading - 3	0			
Sitting and reading - Not done	16.7			
Watching TV - 0	23.3			
Watching TV - 1	33.3			
Watching TV - 2	23.3			
Watching TV - 3	3.3			
Watching TV - Not done	16.7			
Sitting, inactive in a public place - 0	56.7			
Sitting, inactive in a public place - 1	20			
Sitting, inactive in a public place - 2	6.7			
Sitting, inactive in a public place - 3	0			
Sitting, inactive in a public place - Not done	16.7			
Passenger in a car, an hour without break - 0	60			
Passenger in a car, an hour without break - 1	10			
Passenger in a car, an hour without break - 2	6.7			
Passenger in a car, an hour without break - 3	6.7			
Passenger in a car, an hour without break - ND	16.7			
Lying down to rest in the afternoon - 0	13.3			
Lying down to rest in the afternoon - 1	23.3			
Lying down to rest in the afternoon - 2	23.3			
Lying down to rest in the afternoon - 3	23.3			
Lying down to rest in the afternoon - Not done	16.7			
Sitting and talking to someone - 0	76.7			
Sitting and talking to someone - 1	6.7			
Sitting and talking to someone - 2	0			
Sitting and talking to someone - 3	0			
Sitting and talking to someone - Not done	16.7			
Sitting quietly after a lunch without alcohol - 0	30			
Sitting quietly after a lunch without alcohol - 1	23.3			
Sitting quietly after a lunch without alcohol - 2	20			
Sitting quietly after a lunch without alcohol - 3	10			
Sitting quietly after a lunch without alcohol - ND	16.7			
In a car, stopped a few minutes in the traffic - 0	73.3			

In a car, stopped a few minutes in the traffic - 1	10			
In a car, stopped a few minutes in the traffic - 2	0			
In a car, stopped a few minutes in the traffic - 3	0			
In a car, stopped a few minutes in the traffic -ND	16.7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Pasireotide s.c <1200ug/d
Reporting group description:	
Pasireotide s.c <1200ug/d	
Reporting group title	Pasireotide s.c 1200-<1500ug/d
Reporting group description:	
Pasireotide s.c 1200-<1500ug/d	
Reporting group title	Pasireotide s.c 1500ug/d and above
Reporting group description:	
Pasireotide s.c 1500ug/d and above	
Reporting group title	Pasireotide s.c Overall
Reporting group description:	
Pasireotide s.c Overall	

Serious adverse events	Pasireotide s.c <1200ug/d	Pasireotide s.c 1200-<1500ug/d	Pasireotide s.c 1500ug/d and above
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	4 / 30 (13.33%)	2 / 12 (16.67%)
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)			
Mucoepidermoid carcinoma			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Tracheal obstruction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 12 (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

Eye disorders			
Blindness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 12 (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			
Cholecystitis chronic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 12 (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
Endocrine disorders			
Acromegaly			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 12 (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
Osteoarthritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 12 (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			
Laryngitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 12 (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
Tracheobronchitis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 12 (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
Pilonidal cyst			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
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			
Diabetes mellitus			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 12 (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
Hyperglycaemia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Pasireotide s.c Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 30 (26.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mucoepidermoid carcinoma			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Tracheal obstruction			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Acromegaly			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Laryngitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pilonidal cyst			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pasireotide s.c <1200ug/d	Pasireotide s.c 1200- <1500ug/d	Pasireotide s.c 1500ug/d and above
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 30 (70.00%)	25 / 30 (83.33%)	11 / 12 (91.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Chest pain			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Oedema peripheral			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	3 / 30 (10.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Chills			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 30 (10.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Insomnia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Blood lactate dehydrogenase increased			

subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Blood pressure increased subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Weight decreased subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 2	1 / 30 (3.33%) 2	0 / 12 (0.00%) 0
Injury, poisoning and procedural complications Incision site pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Congenital, familial and genetic disorders Hydrocele subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3	4 / 30 (13.33%) 4	0 / 12 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3	2 / 30 (6.67%) 2	0 / 12 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 4	4 / 30 (13.33%) 6	1 / 12 (8.33%) 2
Restless legs syndrome subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	1 / 12 (8.33%) 1
Tremor subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 30 (6.67%) 2	0 / 12 (0.00%) 0
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3	1 / 30 (3.33%) 1	3 / 12 (25.00%) 3
Pancytopenia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 30 (3.33%) 2	0 / 12 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 7	2 / 30 (6.67%) 3	2 / 12 (16.67%) 3
Flatulence subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 6	3 / 30 (10.00%) 3	0 / 12 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	10 / 30 (33.33%) 16	11 / 30 (36.67%) 17	5 / 12 (41.67%) 7
Constipation subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3	2 / 30 (6.67%) 2	1 / 12 (8.33%) 1
Nausea subjects affected / exposed occurrences (all)	9 / 30 (30.00%) 12	10 / 30 (33.33%) 13	1 / 12 (8.33%) 2
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 30 (6.67%) 2	0 / 12 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 30 (6.67%) 2	0 / 12 (0.00%) 0
Oesophageal spasm			

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 4	2 / 30 (6.67%) 2	1 / 12 (8.33%) 1
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Alopecia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	2 / 30 (6.67%) 2	0 / 12 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Hyperhidrosis subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	3 / 30 (10.00%) 5	0 / 12 (0.00%) 0
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 4	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 30 (6.67%) 2	1 / 12 (8.33%) 1
Endocrine disorders Diabetes insipidus subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	4 / 30 (13.33%) 9	0 / 12 (0.00%) 0
Back pain			

subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	2 / 12 (16.67%)
occurrences (all)	2	4	3
Arthritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Jaw disorder			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Muscle spasms			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Osteoarthritis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Tendonitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 30 (10.00%)	2 / 30 (6.67%)	2 / 12 (16.67%)
occurrences (all)	3	2	2
Burn infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1

Influenza			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	1 / 12 (8.33%)
occurrences (all)	0	5	1
Nasopharyngitis			
subjects affected / exposed	3 / 30 (10.00%)	3 / 30 (10.00%)	2 / 12 (16.67%)
occurrences (all)	4	6	2
Otitis externa			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Tooth infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 30 (0.00%)	4 / 30 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	0 / 12 (0.00%)
occurrences (all)	2	3	0
Hypoglycaemia			

subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	2	3	0

Non-serious adverse events	Pasireotide s.c Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Chills			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Reproductive system and breast disorders			

Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Respiratory, thoracic and mediastinal disorders Sleep apnoea syndrome subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 4 2 / 30 (6.67%) 3		
Investigations Blood glucose increased subjects affected / exposed occurrences (all) Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) Blood pressure increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3 2 / 30 (6.67%) 2 1 / 30 (3.33%) 1 2 / 30 (6.67%) 4		
Injury, poisoning and procedural complications Incision site pain subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2 2 / 30 (6.67%) 2		
Congenital, familial and genetic disorders			

Hydrocele subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 7		
Paraesthesia subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Headache subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 12		
Restless legs syndrome subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Tremor subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 7		
Pancytopenia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Gastrointestinal disorders Abdominal pain			

subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	13		
Flatulence			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	15 / 30 (50.00%)		
occurrences (all)	40		
Constipation			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	15 / 30 (50.00%)		
occurrences (all)	27		
Haemorrhoids			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Oesophageal spasm			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Eczema			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	5		
Nephrolithiasis			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	10		
Back pain			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	9		
Arthritis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Jaw disorder			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Osteoarthritis			

subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Tendonitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Burn infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	12		
Otitis externa			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		

Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Tooth infection subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Metabolism and nutrition disorders			
Diabetes mellitus subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 5		
Hypoglycaemia subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2007	• The enrollment of patients into this extension study had closed; however, treatment of patients receiving clinical benefit was to be continued until pasireotide s.c. was commercially available or the development program was discontinued, whichever came first. As pasireotide had been well tolerated by patients with acromegaly, the visit schedule previously defined in the protocol was revised from one visit per month to one visit every three months. A 3-month interval was considered sufficient to adequately monitor safety and efficacy in this study. • Increases in blood glucose during treatment with pasireotide s.c. had been observed in previous studies. However, the increases were moderate and generally well managed by adjustment in oral hypoglycemic medications or the initiation of insulin therapy. Thus, some guidance on monitoring and the management of blood glucose levels was also added to the protocol by this amendment. • Blood samples were no longer collected for PK or biomarker development studies. • The visit schedule was amended to add urinalysis assessment, to be consistent with the assessments required by the study protocol. • In addition, editorial changes to the cover page of the protocol were made to meet regulatory requirements.
28 April 2010	Based on results obtained from the thorough QT/QTc study, which provided data on the QT/QTc intervals of a supra-therapeutic dose of pasireotide in healthy volunteers, additional ECG monitoring was implemented in ongoing pasireotide studies to further strengthen the safety of patients. Instead of recording ECGs every six months in the extension period, on implementation of the amendment, ECGs were to be recorded every three months. • In addition, the study discontinuation criteria and text on use of concomitant medications were modified to include consideration of QT measurements.
12 December 2011	• Include additional hepatic-related safety parameters as a result of an internal hepatic medical review of pasireotide study's. Hepatic related discontinuation criteria and hepatic safety management criteria were included.
13 June 2012	Correct the assessment of laboratory samples, ECGs, and CT or MRI scan to match with the core study protocol as the extension protocol incorrectly stated local assessment. These were to be assessed centrally and results were to be transferred electronically to Novartis. • In addition clarification was provided to remove the PT (INR) collection from the blood chemistry panel. This test was only to be done if the patient meets the abnormal liver function criteria. It was not to be considered as part of routine blood chemistry panel.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported