Clinical trial results:
A multi-center, intra-patient dose escalation Phase II study to evaluate the preliminary efficacy, safety and pharmacokinetics of pasireotide (SOM230) subcutaneous (sc) followed by pasireotide LAR in patients with dumping syndrome

Summary

EudraCT number	2012-001534-34
Trial protocol	BE NL
Global end of trial date	07 August 2015

Results information

Result version number	v1 (current)
This version publication date	15 August 2016
First version publication date	15 August 2016

Trial information

Trial identification

Sponsor protocol code	CSOM230X2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01637272
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	07 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the treatment effect of pasireotide sc on plasma glucose levels during a 3-hour oral glucose tolerance test (OGTT) at the end of sc dose escalation phase.

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	08 January 2013
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: 11
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	43
EEA total number of subjects	31

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)	42
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

43 patients were enrolled as planned; 33 patients completed the core sc phase, 31 patients completed the core LAR phase. Of the 31 patients who completed core LAR phase, 27 patients entered the extension phase. Of the 27 patients who entered the extension phase, 23 patients completed the study.

Pre-assignment

Screening details:

All patients underwent an OGTT (75g of glucose) and were evaluated at different time points. If the glucose level was <60 mg/dL at 90, 120, 150 or 180 min during the OGTT and all the other eligibility criteria were met, patients were allowed to start study medication. The study was divided in 2 phases, core phase and extension phase.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	SOM230

Arm description:

Subjects with dumping syndrome treated with pasireotide sc followed by pasireotide LAR

Arm type	Experimental
Investigational medicinal product name	Pasireotide
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

Pasireotide (SOM230) sc injection: was provided as solution for injection in individual one-point-cut 1 mL ampule, containing nominally 200 µg of pasireotide. Pasireotide (SOM230) im LAR depot injection was provided as micro particles powder in vials containing nominally 10, 20, 40 and 60 mg of pasireotide (as free base) and solvent for suspension for injection in ampules for the reconstitution of the LAR micro particles.

Number of subjects in period 1	SOM230
Started	43
Completed	23
Not completed	20
Consent withdrawn by subject	3
Adverse event, non-fatal	6
Unsatisfactory therapeutic effect	2
completed core, did not enter ext. phase	4
Administrative problems	1
Lost to follow-up	2

Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	SOM230
Reporting group description:	
Subjects with dumping syndrome treated with pasireotide sc followed by pasireotide LAR	

Reporting group values	SOM230	Total	
Number of subjects	43	43	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	42	42	
From 65-84 years	1	1	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	45.9		
standard deviation	± 9.99	-	
Gender, Male/Female Units: Participants			
Female	38	38	
Male	5	5	

End points

End points reporting groups

Reporting group title	SOM230
Reporting group description:	
Subjects with dumping syndrome treated with pasireotide sc followed by pasireotide LAR	

Primary: Response rate in plasma glucose level at the end of subcutaneous (s.c.) dose escalation phase

End point title	Response rate in plasma glucose level at the end of subcutaneous (s.c.) dose escalation phase[1]
End point description:	
Response rate is defined as percentage of patients with no glucose values < 60 mg/dL at 90,120, 150 and 180 min during the Oral Glucose Tolerance Test (OGTT) at the end of s.c. dose escalation phase. No statistical analysis was planned for this primary outcome.	
End point type	Primary
End point timeframe:	
at month 3	

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 statistical analysis was planned for this primary outcome.

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: percentage of participants				
number (confidence interval 95%)	60.5 (44.41 to 75.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate in plasma glucose level at the end of 12 months (extension phase)

End point title	Response rate in plasma glucose level at the end of 12 months (extension phase)
End point description:	
Response rate is defined as percentage of patients with no glucose values < 60 mg/dL at 90,120, 150 and 180 min during the Oral Glucose Tolerance Test (OGTT) at the end of 12 months (extension phase)	
End point type	Secondary
End point timeframe:	
at month 12	

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: percentage of participants				
number (confidence interval 95%)	39.4 (22.91 to 57.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate in pulse rate at end of Month 12 (extension phase)

End point title	Response rate in pulse rate at end of Month 12 (extension phase)

End point description:

Pulse rate was defined as percentage of patients with change in pulse rate <10 bpm from pre-OGTT to 30 minutes during the 3 hour OGTT at Month 12.

End point type	Secondary

End point timeframe:

at end of month 12

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (not applicable)				
< 10 bits per minute (bpm)	75.8			
>= 10bpm	24.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate in hematocrit level at the end of the Month 12 (extension phase)

End point title	Response rate in hematocrit level at the end of the Month 12 (extension phase)

End point description:

Percentage of patients with change in hematocrit < 3% from pre-OGTT to 30 min during the OGTT at month 12

End point type	Secondary

End point timeframe:

at the end of Month 12

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (not applicable)				
< 3%	78.8			
>= 3%	21.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin levels at the end of the Month 12 (extension phase)

End point title	Insulin levels at the end of the Month 12 (extension phase)

End point description:

Percentage changes of insulin at the end of Month 12 from end of Month 3 at different time points.

End point type	Secondary

End point timeframe:

Month 3 (M3), Month 12 (M12)

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: pmol/L				
arithmetic mean (standard deviation)				
Pre-OGTT at M3 (n=30)	37.6 (± 24.74)			
30 Minutes at M3 (n=29)	197 (± 257.55)			
60 Minutes at M3 (n= 30)	369.2 (± 360.67)			
90 Minutes at M3 (n=30)	316.4 (± 265.25)			
120 Minutes at M3 (n=31)	188.5 (± 211.6)			
150 Minutes at M3 (n=32)	105.6 (± 168.77)			
180 Minutes at M3 (n=31)	59.7 (± 53.02)			
Pre-OGTT at M12 (n =21)	29 (± 14.43)			
30 Minutes at M12 (n=23)	294.1 (± 177.25)			
60 Minutes at M12 (n=22)	602.1 (± 381.09)			
90 Minutes at M12 (n=22)	472 (± 438.82)			
120 Minutes at M12 (n=22)	195.1 (± 247.43)			

150 Minutes at M12 (n=22)	76 (± 106.05)			
180 Minutes at M12 (n=22)	52 (± 58.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Glucagon levels at the end Month 12 (extension phase)

End point title	Glucagon levels at the end Month 12 (extension phase)

End point description:

Percentage changes of glucagon at the end of Month 12 (extension phase) from end of Month 3 at different time points.

End point type	Secondary

End point timeframe:

Month 3 (M3), Month 12 (M12)

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: pmol/L				
arithmetic mean (standard deviation)				
Pre-OGTT at M3 (n=30)	20.4 (± 6.02)			
30 Minutes at M3 (n=32)	20.7 (± 7.14)			
60 Minutes at M3 (n= 32)	20.9 (± 7.44)			
90 Minutes at M3 (n=31)	20.1 (± 8.03)			
120 Minutes at M3 (n=31)	19.7 (± 7.49)			
150 Minutes at M3 (n=31)	19.9 (± 7.29)			
180 Minutes at M3 (n=31)	20 (± 7.18)			
Pre-OGTT at M12 (n =23)	21.4 (± 6.82)			
30 Minutes at M12 (n=22)	23.8 (± 6.97)			
60 Minutes at M12 (n=22)	22.9 (± 7.07)			
90 Minutes at M12 (n=22)	21.5 (± 7.69)			
120 Minutes at M12 (n=22)	22 (± 7.31)			
150 Minutes at M12 (n=22)	21.8 (± 7.27)			
180 Minutes at M12 (n=22)	22.3 (± 6.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Glucagon-like peptide 1 (GLP-1) levels at the end of Month 12 (extension phase)

End point title	Glucagon-like peptide 1 (GLP-1) levels at the end of Month

	12 (extension phase)

End point description:

Percentage changes of Glucagon-like peptide 1 (GLP-1) at the end of the Month 12 (extension phase) from end of Month 3 at different time points.

End point type	Secondary

End point timeframe:

Month 3 (M3), Month 12 (M12)

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: pmol/L				
arithmetic mean (standard deviation)				
Pre-OGTT at M3 (n=30)	2.9 (± 2.11)			
30 Minutes at M3 (n=31)	12.7 (± 6.71)			
60 Minutes at M3 (n= 31)	11.2 (± 11.31)			
90 Minutes at M3 (n=30)	6.8 (± 4.98)			
120 Minutes at M3 (n=30)	4.9 (± 4.1)			
150 Minutes at M3 (n=30)	3.5 (± 2.34)			
180 Minutes at M3 (n=30)	2.9 (± 1.96)			
Pre-OGTT at M12 (n =23)	1.6 (± 1.26)			
30 Minutes at M12 (n=22)	17.4 (± 17.64)			
60 Minutes at M12 (n=22)	12.6 (± 8.76)			
90 Minutes at M12 (n=22)	7.2 (± 3.71)			
120 Minutes at M12 (n=22)	5 (± 2.98)			
150 Minutes at M12 (n=22)	3.7 (± 2.46)			
180 Minutes at M12 (n=22)	3.2 (± 2.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Gastric Inhibitory Polypeptide (GIP) levels at the end of Month 12 (extension phase)

End point title	Gastric Inhibitory Polypeptide (GIP) levels at the end of Month 12 (extension phase)

End point description:

Percentage changes of Gastric Inhibitory Polypeptide (GIP) at the end of Month 12 (extension phase) from end of Month 3 at different time points.

End point type	Secondary

End point timeframe:

Month 3 (M3), Month 12 (M12)

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: pmol/L				
arithmetic mean (standard deviation)				
Pre-OGTT at M3 (n=30)	2.6 (± 1.77)			
30 Minutes at M3 (n=31)	15.3 (± 10.59)			
60 Minutes at M3 (n= 31)	9.4 (± 6.28)			
90 Minutes at M3 (n=30)	4.1 (± 2.95)			
120 Minutes at M3 (n=30)	2 (± 1.48)			
150 Minutes at M3 (n=29)	1.4 (± 1.23)			
180 Minutes at M3 (n=30)	1.2 (± 1.23)			
Pre-OGTT at M12 (n =23)	1.7 (± 1.51)			
30 Minutes at M12 (n=22)	24.8 (± 18.88)			
60 Minutes at M12 (n=22)	11.6 (± 9.05)			
90 Minutes at M12 (n=22)	5.2 (± 5.18)			
120 Minutes at M12 (n=22)	3 (± 2.81)			
150 Minutes at M12 (n=22)	1.9 (± 1.44)			
180 Minutes at M12 (n=22)	2.5 (± 3.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of live (HRQoL) Short Form- 36 (SF-36) Score(s) at the end of Month 12 (extension phase)

End point title	Health-related quality of live (HRQoL) Short Form- 36 (SF-36) Score(s) at the end of Month 12 (extension phase)

End point description:

Change in HRQoL SF-36 Score(s) at end of the Month 12 (extension phase) from s.c. baseline. SF-36, a 36-Item Short Form Health Survey (SF-36) is a set of generic, coherent, and easily administered quality-of-life measures. These measures rely upon patient self-reporting. Items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved.

End point type	Secondary

End point timeframe:

s.c. baseline Month 12

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage change in HRQoL SF-36 Score				
arithmetic mean (standard deviation)				
s.c. baseline - Physical Functioning (n=33)	44.038 (± 9.0587)			

Month 12 - Physical Functioning (n=23)	46.505 (± 8.5105)			
s.c. baseline - Mental Functioning (n=33)	41.162 (± 11.011)			
Month 12 - Mental Functioning (n=23)	47.021 (± 11.5053)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dumping Score Questionnaire (DSQ) at the end of Month 12 (extension phase)

End point title	Dumping Score Questionnaire (DSQ) at the end of Month 12 (extension phase)

End point description:

Change in Dumping Score Questionnaire at the end of Month 12 (extension phase) from s.c. baseline. DSQ is a disease specific patient reported outcome (PRO) scale that was developed according to the FDA and EMEA guidelines. The questionnaire utilizes a 5-point Likert scale (0, none; 1, mild; 2, moderate; 3, severe; and 4, very severe) to ask a patient to evaluate the intensity of 10 early dumping symptoms (within 30 minutes (<30 minutes) after food ingestion). In addition, the questionnaire also evaluates 5 late dumping symptoms (more than 1.5 hours (>90 minutes) after food ingestion). An early and late dumping score is calculated by adding the severities of all early and late dumping symptoms, respectively. A cumulative dumping score is obtained by adding early and late scores.

End point type	Secondary

End point timeframe:

s.c. baseline, Month 12

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage change in DSQ				
arithmetic mean (standard deviation)				
s.c. baseline - Early symptoms (n=13)	14.2 (± 10.26)			
s.c. baseline - Late symptoms (n=13)	6.7 (± 5.6)			
s.c. baseline - Overall score (n=13)	20.9 (± 15.22)			
M12 - Early symptoms (n=23)	10.7 (± 10.94)			
M12 - Late symptoms (n=23)	5.7 (± 5.93)			
M12 - Overall Score (n=23)	16.3 (± 16.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dumping Severity Score (DSS) at Month 12 (end of the extension phase)

End point title	Dumping Severity Score (DSS) at Month 12 (end of the

	extension phase)

End point description:

Change in Dumping Severity Score at the end of Month 12 (extension phase) from s.c. baseline. At study start patients were assessed using DSS (older version of DSQ); however after the implementation of protocol amendment 2, all patients were expected to use DSQ. Dumping Severity Score was developed by based on symptom pattern descriptions in the literature. The questionnaire utilizes a 4-point Likert scale to ask a patient to evaluate the intensity of 8 early dumping symptoms (within 1 hour after food ingestion) on a scale, 0–3; (0, absent; 1, mild; 2, relevant; and 3, severe), In addition, the questionnaire also evaluates 6 late dumping symptoms (more than 1 hour after food ingestion). An early and late dumping severity score is calculated by adding the severities of all early and late dumping symptoms, respectively. A cumulative dumping severity score is obtained by adding early and late scores. The last patient that answered the DSS was at month 8.

End point type	Secondary

End point timeframe:

s.c. baseline, Month 8

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage change in DSS				
arithmetic mean (standard deviation)				
s.c. baseline - Early symptoms (n=21)	10.6 (± 5.85)			
s.c. baseline - Late symptoms (n=21)	8.9 (± 4.12)			
s.c. baseline - Overall Score (n=21)	19.5 (± 9.36)			
M8 - Early symptoms (n=2)	9 (± 8.49)			
M8 - Late symptoms (n=2)	6 (± 4.24)			
M8 - Overall Score (n=2)	15 (± 12.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment at the end of Month 12 (extension phase)

End point title	Patient Global Assessment at the end of Month 12 (extension phase)

End point description:

Treatment with pasireotide LAR (both early and late dumping scores), was assessed by patient global assessment.

End point type	Secondary

End point timeframe:

s.c. baseline, Month 12

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of participants				
arithmetic mean (standard deviation)				
s.c. baseline (n=31) Month 12 (n=23)	3.9 (± 0.54) 5.9 (± 0.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) parameter: Ctrough d28 associated with each LAR injection at steady state

End point title	Pharmacokinetic (PK) parameter: Ctrough d28 associated with each LAR injection at steady state

End point description:

Assess PK of pasireotide (in extension phase) with monthly injections of 10, 20, 30 40 mg. Due to one patient at LAR 40 mg, Ctrough, ss for this patient is not provided as it is in listings only.

End point type	Secondary

End point timeframe:

Month 12

End point values	SOM230			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: ng/mL				
arithmetic mean (standard deviation)				
LAR 10 mg (n=6) LAR 20 mg (n=6) LAR 30 mg (n=6)	3.34 (± 1.52) 3.76 (± 1.48) 8.19 (± 3.22)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	s.c. phase
Reporting group description:	
s.c. phase	
Reporting group title	LAR phase
Reporting group description:	
LAR phase	
Reporting group title	Overall
Reporting group description:	
Overall	

Serious adverse events	s.c. phase	LAR phase	Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 43 (13.95%)	10 / 33 (30.30%)	12 / 43 (27.91%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Visual field defect			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 43 (2.33%)	0 / 33 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			

subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	2 / 43 (4.65%)	0 / 33 (0.00%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 43 (2.33%)	0 / 33 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Subdiaphragmatic abscess			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	2 / 43 (4.65%)	1 / 33 (3.03%)	3 / 43 (6.98%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 43 (0.00%)	1 / 33 (3.03%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	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	s.c. phase	LAR phase	Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 43 (72.09%)	25 / 33 (75.76%)	34 / 43 (79.07%)
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 43 (2.33%)	2 / 33 (6.06%)	3 / 43 (6.98%)
occurrences (all)	1	2	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 43 (11.63%)	4 / 33 (12.12%)	8 / 43 (18.60%)
occurrences (all)	5	5	9
Chills			
subjects affected / exposed	1 / 43 (2.33%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	3	3	6
Fatigue			
subjects affected / exposed	3 / 43 (6.98%)	8 / 33 (24.24%)	10 / 43 (23.26%)
occurrences (all)	3	8	11
Injection site irritation			
subjects affected / exposed	2 / 43 (4.65%)	1 / 33 (3.03%)	3 / 43 (6.98%)
occurrences (all)	2	1	3
Injection site pain			
subjects affected / exposed	4 / 43 (9.30%)	1 / 33 (3.03%)	5 / 43 (11.63%)
occurrences (all)	4	1	5
Injection site reaction			

subjects affected / exposed	3 / 43 (6.98%)	0 / 33 (0.00%)	3 / 43 (6.98%)
occurrences (all)	3	0	3
Oedema peripheral			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Thirst			
subjects affected / exposed	3 / 43 (6.98%)	0 / 33 (0.00%)	3 / 43 (6.98%)
occurrences (all)	3	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 43 (4.65%)	1 / 33 (3.03%)	3 / 43 (6.98%)
occurrences (all)	2	1	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Depressed mood			
subjects affected / exposed	1 / 43 (2.33%)	2 / 33 (6.06%)	3 / 43 (6.98%)
occurrences (all)	1	2	3
Depression			
subjects affected / exposed	3 / 43 (6.98%)	1 / 33 (3.03%)	3 / 43 (6.98%)
occurrences (all)	3	1	3
Insomnia			
subjects affected / exposed	0 / 43 (0.00%)	3 / 33 (9.09%)	3 / 43 (6.98%)
occurrences (all)	0	3	3
Investigations			
Weight increased			
subjects affected / exposed	3 / 43 (6.98%)	2 / 33 (6.06%)	5 / 43 (11.63%)
occurrences (all)	3	2	5
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 43 (0.00%)	3 / 33 (9.09%)	3 / 43 (6.98%)
occurrences (all)	0	3	3
Fall			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2

Post-traumatic pain			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Rib fracture			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 43 (6.98%)	0 / 33 (0.00%)	3 / 43 (6.98%)
occurrences (all)	3	0	3
Palpitations			
subjects affected / exposed	3 / 43 (6.98%)	0 / 33 (0.00%)	3 / 43 (6.98%)
occurrences (all)	4	0	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 43 (9.30%)	0 / 33 (0.00%)	4 / 43 (9.30%)
occurrences (all)	7	0	7
Headache			
subjects affected / exposed	10 / 43 (23.26%)	9 / 33 (27.27%)	15 / 43 (34.88%)
occurrences (all)	15	9	24
Syncope			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 43 (9.30%)	1 / 33 (3.03%)	4 / 43 (9.30%)
occurrences (all)	4	2	6
Abdominal pain			
subjects affected / exposed	7 / 43 (16.28%)	7 / 33 (21.21%)	9 / 43 (20.93%)
occurrences (all)	10	13	23
Abdominal pain upper			
subjects affected / exposed	5 / 43 (11.63%)	3 / 33 (9.09%)	8 / 43 (18.60%)
occurrences (all)	6	3	9

Constipation			
subjects affected / exposed	3 / 43 (6.98%)	0 / 33 (0.00%)	3 / 43 (6.98%)
occurrences (all)	3	0	3
Diarrhoea			
subjects affected / exposed	9 / 43 (20.93%)	8 / 33 (24.24%)	12 / 43 (27.91%)
occurrences (all)	12	17	28
Dyspepsia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Nausea			
subjects affected / exposed	6 / 43 (13.95%)	6 / 33 (18.18%)	10 / 43 (23.26%)
occurrences (all)	7	7	14
Steatorrhoea			
subjects affected / exposed	4 / 43 (9.30%)	0 / 33 (0.00%)	4 / 43 (9.30%)
occurrences (all)	4	0	4
Vomiting			
subjects affected / exposed	3 / 43 (6.98%)	3 / 33 (9.09%)	5 / 43 (11.63%)
occurrences (all)	7	4	11
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 43 (0.00%)	5 / 33 (15.15%)	5 / 43 (11.63%)
occurrences (all)	0	8	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Hyperhidrosis			
subjects affected / exposed	3 / 43 (6.98%)	2 / 33 (6.06%)	4 / 43 (9.30%)
occurrences (all)	3	2	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 43 (6.98%)	4 / 33 (12.12%)	6 / 43 (13.95%)
occurrences (all)	3	5	8
Muscle spasms			
subjects affected / exposed	2 / 43 (4.65%)	4 / 33 (12.12%)	5 / 43 (11.63%)
occurrences (all)	4	4	8

Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 43 (2.33%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	1	2	3
Gastroenteritis			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Nasopharyngitis			
subjects affected / exposed	3 / 43 (6.98%)	6 / 33 (18.18%)	8 / 43 (18.60%)
occurrences (all)	3	6	9
Sinusitis			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	3	3
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 43 (4.65%)	3 / 33 (9.09%)	5 / 43 (11.63%)
occurrences (all)	2	3	5
Hypoglycaemia			
subjects affected / exposed	5 / 43 (11.63%)	9 / 33 (27.27%)	12 / 43 (27.91%)
occurrences (all)	7	12	19
Hypophosphataemia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 33 (6.06%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Iron deficiency			
subjects affected / exposed	2 / 43 (4.65%)	5 / 33 (15.15%)	6 / 43 (13.95%)
occurrences (all)	2	5	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2012	The purpose of this amendment was to increase the duration of contraception after the last dose of the study drug for both formulations: pasireotide sc (1 month) and pasireotide LAR (3 months) to ensure patient's safety should they plan to conceive. In addition, an exclusion criterion was added to ensure that potentially unreliable or vulnerable subjects (e.g. person kept in detention) and those judged by the Investigator to be unsuitable for the study were not included in the protocol. Additionally, since some patients with dumping syndrome can present with hypoglycemia at 90 minutes after receiving the 75 g of glucose during an OGTT, the protocol was updated to allow for the inclusion of these patients.
28 March 2013	The purpose of this amendment was to update the Dumping Score Questionnaire (DSQ). The Dumping Severity Score (DSS) is an instrument to evaluate the intensity of DS symptoms based on a 4-point Likert scale 1 hour after and more than 1 hour after digestion). Upon thorough data safety (DS) expert panel review of the DSS, the instrument was updated to consider measurements that were more sensitive to DS symptoms and a 5-point scale was included. The development and validation of the DSQ according to the FDA and EMEA guidelines was planned at the study inception and was performed in parallel with protocol development. The first phase of the DSQ development was completed while the study was ongoing and some changes were incorporated into the questionnaire. After this amendment all patients were to assessed with the DSQ instead of DSS. An additional purpose of this amendment was to extend the duration of the follow up period for a newborn of a patient who becomes pregnant during the study (from Day 0 to Month 3 after delivery) to be in alignment with the current ICF.
04 December 2013	The purpose of this amendment was to add an additional option to prepare 30 mg pasireotide LAR dosage strength using 1 x 20 mg + 1 x 40 mg vials due to unforeseen drug allocation issues. In an effort to avoid forthcoming amendments due to unpredictable drug supply issues, the IFU for pasireotide sc and pasireotide LAR were removed. These instructions were then provided in a standalone Oncology Clinical Instructions for Use manual titled "Pasireotide

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

All safety parameters were analyzed by study phase (sc/LAR)

Notes: