



Clinical trial results:

An open-label, multi-center, expanded access study of pasireotide s.c. in patients with Cushing's disease

Summary

EudraCT number	2010-024165-44
Trial protocol	DE GR ES CZ NL
Global end of trial date	26 January 2017

Results information

Result version number	v1 (current)
This version publication date	11 February 2018
First version publication date	11 February 2018

Trial information

Trial identification

Sponsor protocol code	CSOM230B2406
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01582061
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to document the safety of pasireotide subcutaneous in patients with Cushing's disease

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	16 August 2011
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	Germany: 15
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Brazil: 17
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	Russian Federation: 2
Worldwide total number of subjects	104
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
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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)	99
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After a 21-day screening period, patients who met the inclusion/exclusion criteria received pasireotide subcutaneous twice a day (BID)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pasireotide 600 µg

Arm description:

Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 600 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 600 µg for glucose impaired metabolism patients. Mean daily dose category is defined on the mean daily dose considering the following grouping rule: 600 µg bid group includes all patients whose mean daily dose < 1500 µg /day.

Arm type	Experimental
Investigational medicinal product name	Pasireotide
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Starting dose was 600 µg bid for all patients in the European Union (EU) and all other countries starting dose was 900 µg bid, however, for patients with impaired glucose metabolism 600 µg bid was the starting dose.

Arm title	Pasireotide 900 µg
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Arm description:

Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 900 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 900 µg. Mean daily dose category is defined on the mean daily dose considering the following grouping rule: 900 µg bid group includes all patients whose mean daily dose ≥ 1500 µg /day

Arm type	Experimental
Investigational medicinal product name	Pasireotide
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Starting dose was 600 µg bid for all patients in the European Union (EU) and all other countries starting dose was 900 µg bid, however, for patients with impaired glucose metabolism 600 µg bid was the starting dose.

Number of subjects in period 1	Pasireotide 600 µg	Pasireotide 900 µg
Started	49	55
Completed	21	19
Not completed	28	36
Abnormal laboratory value(s)	1	-
condition no longer requires study drug	1	-
Adverse event, serious fatal	-	1
Consent withdrawn by subject	10	4
Adverse event, non-fatal	12	8
Lost to follow-up	1	-
Lack of efficacy	3	23

Baseline characteristics

Reporting groups

Reporting group title	Pasireotide 600 µg
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Reporting group description:

Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 600 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 600 µg for glucose impaired metabolism patients. Mean daily dose category is defined on the mean daily dose considering the following grouping rule: 600 µg bid group includes all patients whose mean daily dose < 1500 µg /day.

Reporting group title	Pasireotide 900 µg
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Reporting group description:

Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 900 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 900 µg. Mean daily dose category is defined on the mean daily dose considering the following grouping rule: 900 µg bid group includes all patients whose mean daily dose ≥ 1500 µg /day

Reporting group values	Pasireotide 600 µg	Pasireotide 900 µg	Total
Number of subjects	49	55	104
Age categorical Units: Subjects			
Adults (18-64 years)	46	53	99
From 65-84 years	3	2	5
Age Continuous Units: years			
arithmetic mean	45.5	39.9	
standard deviation	± 13.14	± 12.55	-
Sex: Female, Male Units: Subjects			
Female	37	47	84
Male	12	8	20
Race (NIH/OMB) Units: Subjects			
Asian	6	15	21
Black or African American	3	2	5
White	39	36	75
Unknown or Not Reported	1	2	3

End points

End points reporting groups

Reporting group title	Pasireotide 600 µg
Reporting group description: Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 600 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 600 µg for glucose impaired metabolism patients. Mean daily dose category is defined on the mean daily dose considering the following grouping rule: 600 µg bid group includes all patients whose mean daily dose < 1500 µg /day.	
Reporting group title	Pasireotide 900 µg
Reporting group description: Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 900 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 900 µg. Mean daily dose category is defined on the mean daily dose considering the following grouping rule: 900 µg bid group includes all patients whose mean daily dose ≥ 1500 µg /day	
Subject analysis set title	600 µg bid - all grades
Subject analysis set type	Sub-group analysis
Subject analysis set description: All grades of adverse events. Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 600 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 600 µg for glucose impaired metabolism patients. Mean daily dose category is defined: 600 µg bid group includes all patients whose mean daily dose < 1500 µg /day.	
Subject analysis set title	600 µg - grades 3/4
Subject analysis set type	Sub-group analysis
Subject analysis set description: Adverse event grades 3 and 4. Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 600 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 600 µg for glucose impaired metabolism patients	
Subject analysis set title	900 µg - all grades
Subject analysis set type	Sub-group analysis
Subject analysis set description: All grades of adverse events. Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 900 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 900 µg. Mean daily dose category is defined : 900 µg bid group includes all patients whose mean daily dose ≥ 1500 µg /day	
Subject analysis set title	900 µg - grades 3/4
Subject analysis set type	Sub-group analysis
Subject analysis set description: Adverse event grades 3 and 4. Pasireotide sub-cutaneous was supplied in 1 ml ampoules containing 900 µg pasireotide per 1 ml of solution and was administered BID. Starting dose was 900 µg	
Subject analysis set title	All patients - all grades
Subject analysis set type	Sub-group analysis
Subject analysis set description: All grades of adverse events for all patients who received 600 µg bid or 900 µg bid of pasireotide sub-cutaneous.	
Subject analysis set title	All patients - grades 3/4
Subject analysis set type	Sub-group analysis
Subject analysis set description: Grades 3 and 4 of adverse events for all patients who received 600 µg bid or 900 µg bid of pasireotide sub-cutaneous.	
Subject analysis set title	All patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients received pasireotide 600 µg or 900 µg BID	
Subject analysis set title	All patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients received pasireotide 600 µg or 900 µg BID

Subject analysis set title	All patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients received pasireotide 600 µg or 900 µg BID

Primary: Percentage of patients with a drug-related adverse event that is recorded as grade 3 or 4 or as a serious adverse event (SAE)

End point title	Percentage of patients with a drug-related adverse event that is recorded as grade 3 or 4 or as a serious adverse event (SAE) ^[1]
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End point description:

Only AEs occurring on or after the start of study treatment and no more than 28 days after the discontinuation of study treatment. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple severity grades for an AE while on a treatment, is only counted under the maximum grade.

End point type	Primary
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End point timeframe:

Baseline up to approximately 256 weeks

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 done.

End point values	600 µg bid - all grades	600 µg - grades 3/4	900 µg - all grades	900 µg - grades 3/4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	26	55	15
Units: percentage of participants				
number (not applicable)				
Any primary system organ class	53.1	53.1	29.1	27.3
Metabolism and nutrition disorders	26.5	26.5	12.7	10.9
Gastrointestinal disorders	18.4	18.4	7.3	7.3
Investigations	8.2	8.2	3.6	3.6
Hepatobiliary disorders	2.0	2.0	5.5	5.5
Endocrine disorders	6.1	6.1	0	0
Gen disorders,admin site conditions	4.1	4.1	0	0
Ear and labyrinth disorders	2.0	2.0	0	0
Infections and infestations	2.0	2.0	0	0
Musculoskeletal and connective tissue disorders	2.0	2.0	0	0
Neoplasms benign, malignant and unspecified	2.0	2.0	0	0
Nervous system disorders	2.0	2.0	0	0
Psychiatric disorders	0	0	1.8	1.8
Respiratory, thoracic, mediastinal disorders	0	0	1.8	0

End point values	All patients - all grades	All patients - grades 3/4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	104	41		

Units: percentage of participants				
number (not applicable)				
Any primary system organ class	40.4	39.4		
Metabolism and nutrition disorders	19.2	18.3		
Gastrointestinal disorders	12.5	12.5		
Investigations	5.8	5.8		
Hepatobiliary disorders	3.8	3.8		
Endocrine disorders	2.9	2.9		
Gen disorders,admin site conditions	1.9	1.9		
Ear and labyrinth disorders	1.0	1.0		
Infections and infestations	1.0	1.0		
Musculoskeletal and connective tissue disorders	1.0	1.0		
Neoplasms benign, malignant and unspecified	1.0	1.0		
Nervous system disorders	1.0	1.0		
Psychiatric disorders	1.0	1.0		
Respiratory, thoracic, mediastinal disorders	1.0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with mean Urinary Free Cortisol (UFC) ≤ Upper Limit of Normal (ULN)

End point title	Percentage of patients with mean Urinary Free Cortisol (UFC) ≤ Upper Limit of Normal (ULN)
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End point description:

The 24h-UFC concentration results from three samples during screening were averaged to obtain baseline. After baseline, mean 24h UFC was determined at week 24. At Week 4, 8, 16 and 20, mean 24h UFC was determined from two 24 hour urine collections collected on two consecutive days occurring before the visit. At Week 12, 24 and 48, the mean 24h-UFC from three 24 hour urine collections, collected over the week before the visit, was determined. After Week 24, the mean 24h UFC was determined at 12-week intervals until end of study visit, from two 24 hour collections during two consecutive days prior to each respective visit (except at Week 48). UFC was determined by liquid chromatography tandem mass spectroscopy (LC/MS/MS). The normal ranges were determined by the central laboratory's own reference range. All samples, including screening samples, were analyzed by a central laboratory.

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percentage of participants				
number (confidence interval 95%)				
Week 12	77.8 (57.74 to 91.38)	38.5 (23.36 to 55.38)	54.5 (41.81 to 66.86)	

Week 24	68.2 (45.13 to 86.14)	29.2 (12.62 to 51.09)	47.8 (32.89 to 63.05)	
Week 48	70.0 (34.75 to 93.33)	18.2 (2.28 to 51.78)	42.9 (21.82 to 65.98)	
Week 24 (LOCF)	54.1 (36.92 to 70.51)	28.6 (16.59 to 43.26)	39.5 (29.15 to 50.66)	
Week 48 (LOCF)	51.4 (34.40 to 68.08)	22.4 (11.78 to 36.62)	34.9 (24.92 to 45.92)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients achieving a reduction of mean UFC \geq 50% from baseline

End point title	Percentage of patients achieving a reduction of mean UFC \geq 50% from baseline
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End point description:

The 24h-UFC concentration results from three samples during screening were averaged to obtain baseline. After baseline, mean 24h UFC was determined at week 24. At Week 4, 8, 16 and 20, mean 24h UFC was determined from two 24 hour urine collections collected on two consecutive days occurring before the visit. At Week 12, 24 and 48, the mean 24h-UFC from three 24 hour urine collections, collected over the week before the visit, was determined. After Week 24, the mean 24h UFC was determined at 12-week intervals until end of study visit, from two 24 hour collections during two consecutive days prior to each respective visit (except at Week 48). UFC was determined by liquid chromatography tandem mass spectroscopy (LC/MS/MS). The normal ranges were determined by the central laboratory's own reference range. All samples, including screening samples, were analyzed by a central laboratory.

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 μ g	Pasireotide 900 μ g	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percentage of participants				
number (confidence interval 95%)				
Week 12	74.1 (53.72 to 88.89)	48.7 (32.42 to 65.22)	59.1 (46.29 to 71.05)	
Week 24	68.2 (45.13 to 86.14)	29.2 (12.62 to 51.09)	47.8 (32.89 to 63.05)	
Week 48	70.0 (34.75 to 93.33)	18.2 (2.28 to 51.78)	42.9 (21.82 to 65.98)	
Week 24 (LOCF)	56.8 (39.49 to 72.90)	38.8 (25.20 to 53.76)	46.5 (35.68 to 57.59)	
Week 48 (LOCF)	51.4 (34.40 to 68.08)	42.9 (28.82 to 57.79)	46.5 (35.68 to 57.59)	

Statistical analyses

Secondary: Percent change in Cushing Quality of Life and Work Productivity and Activity Impairment-General Health (WPAI-GH) scores

End point title	Percent change in Cushing Quality of Life and Work Productivity and Activity Impairment-General Health (WPAI-GH) scores
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End point description:

A 12-item Cushing's syndrome HRQoL questionnaire (CushingQoL, cf. Webb et al 2008) was implemented and patients who completed 9 or more items at a visit were considered evaluable for that visit. The standardized scores were calculated as follows: 1) Obtain raw scores, denoted by X, as the sum of all the ratings on all the HRQoL questions for a single patient and the score can range from 12 (worst HRQoL) to 60 points (best HRQoL). Therefore, the lower the score, greater the negative impact on HRQoL and 2) obtain standardized score, Y, for a single patient • $Y = 100 (X-12) / (60-12) = 100 (X-12)/48$. For example, if a patient answers all 12 items with 'Sometimes' or 'Somewhat', $X = 36$ and $Y = 100 \cdot 24/48 = 50$. The WPAI-GH questionnaire was used to assess work productivity and activity impairment. However, there was very limited baseline data and therefore the results and outcomes of the objective, 'change from baseline in WPAI-GH scores' are not included.

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	47	54	104	
Units: percent change in score				
arithmetic mean (standard deviation)				
Week 12	21.3 (± 47.03)	100.8 (± 252.25)	67.1 (± 197.09)	
Week 24	36.7 (± 59.25)	119.7 (± 321.61)	82.3 (± 243.19)	
Week 48	24.0 (± 37.76)	42.3 (± 60.75)	34.4 (± 52.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Cushing's disease clinical signs and symptoms - blood pressure (BP)

End point title	Percent change in Cushing's disease clinical signs and symptoms - blood pressure (BP)
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End point description:

Standing systolic and diastolic BP based on 1 assessment and sitting systolic and diastolic BP was mean of 3 assessments.

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percent change of mmHg				
arithmetic mean (standard deviation)				
Sitting systolic Week 12	-6.8 (± 12.04)	-1.4 (± 14.40)	-3.8 (± 13.61)	
Sitting systolic Week 24	-7.4 (± 8.97)	-5.7 (± 11.09)	-6.5 (± 10.13)	
Sitting systolic Week 48	-5.1 (± 8.57)	-4.7 (± 12.55)	-4.9 (± 10.87)	
Standing systolic Week 12	-7.9 (± 12.49)	-3.6 (± 15.38)	-5.5 (± 14.27)	
Standing systolic Week 24	-10.9 (± 10.30)	-6.7 (± 14.09)	-8.6 (± 12.62)	
Standing systolic Week 48	-6.5 (± 9.45)	-4.4 (± 13.86)	-5.3 (± 12.10)	
Sitting diastolic Week 12	-4.6 (± 15.13)	-0.2 (± 14.40)	-2.1 (± 14.79)	
Sitting diastolic Week 24	-6.2 (± 7.29)	-3.8 (± 15.83)	-4.9 (± 12.65)	
Sitting diastolic Week 48	-3.3 (± 10.38)	-4.3 (± 13.93)	-3.8 (± 12.37)	
Standing diastolic Week 12	-5.5 (± 16.02)	-1.9 (± 17.63)	-3.5 (± 16.93)	
Standing diastolic Week 24	-7.6 (± 10.30)	-5.3 (± 16.74)	-6.3 (± 14.18)	
Standing diastolic Week 48	-2.1 (± 13.78)	-4.4 (± 14.13)	-3.4 (± 13.83)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Cushing's disease clinical signs and symptoms - pulse

End point title	Percent change in Cushing's disease clinical signs and symptoms - pulse
End point description:	
Change from baseline is shown as: Percent change from baseline (BL) =((Post BL value – BL value)/ BL value)*100	
End point type	Secondary
End point timeframe:	
Baseline, week 12, 24 and 48	

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percent change in bpm				
arithmetic mean (standard deviation)				
Sitting pulse Week 12	2.3 (± 18.93)	-7.5 (± 11.50)	-3.2 (± 15.87)	
Sitting pulse Week 24	-1.8 (± 17.05)	-2.6 (± 18.07)	-2.2 (± 17.46)	
Sitting pulse Week 48	2.9 (± 16.39)	3.7 (± 15.46)	3.3 (± 15.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Cushing's disease clinical signs and symptoms - Temperature

End point title	Percent change in Cushing's disease clinical signs and symptoms - Temperature
End point description: Body temperature in celsius	
End point type	Secondary
End point timeframe: Baseline, week 12, 24 and 48	

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percent change of degrees celsius				
arithmetic mean (standard deviation)				
Week 12	0.1 (± 1.26)	-0.3 (± 1.06)	-0.1 (± 1.17)	
Week 24	-0.1 (± 1.15)	-0.1 (± 1.26)	-0.1 (± 1.20)	
Week 48	0.03 (± 1.47)	-0.1 (± 1.19)	0.1 (± 1.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Cushing's disease clinical signs and symptoms - Body mass index (BMI)

End point title	Percent change in Cushing's disease clinical signs and symptoms - Body mass index (BMI)
End point description: Percent of patients reducing by at least one class level. Class levels: <25.0, 25.0 to <30.0, ≥ 30.0	
End point type	Secondary
End point timeframe: Baseline, week 12, 24 and 48	

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percent change in kg/m2				
arithmetic mean (standard deviation)				
Week 12	-4.2 (± 3.70)	-4.8 (± 5.38)	-4.5 (± 4.69)	
Week 24	-7.3 (± 5.46)	-5.2 (± 6.51)	-6.1 (± 6.10)	
Week 48	-8.0 (± 6.82)	-6.3 (± 7.88)	-7.0 (± 7.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Cushing's disease clinical signs and symptoms - Weight

End point title	Percent change in Cushing's disease clinical signs and symptoms - Weight
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End point description:

Clinically relevant threshold (at any time point) was reduction of $\geq 5\%$

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 μg	Pasireotide 900 μg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percent change in kg				
arithmetic mean (standard deviation)				
Week 12	-4.2 (\pm 3.70)	-4.8 (\pm 5.38)	-4.5 (\pm 4.69)	
Week 24	-7.3 (\pm 5.46)	-5.2 (\pm 6.51)	-6.1 (\pm 6.10)	
Week 48	-8.0 (\pm 6.82)	-6.3 (\pm 7.88)	-7.0 (\pm 7.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Cushing's disease clinical signs and symptoms - Muscle Strength

End point title	Percent change in Cushing's disease clinical signs and symptoms - Muscle Strength
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End point description:

Direct observation of ability to stand unaided: 0=able to stand easily with arms extended, 1=able to stand after several efforts without using arms as assistance, 2=able to stand only by using arms as assistance 3=completely unable to stand

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percent change in scores				
arithmetic mean (standard deviation)				
Week 12	-34.6 (± 62.53)	-53.7 (± 46.98)	-42.4 (± 56.28)	
Week 24	-28.6 (± 48.80)	-47.6 (± 50.40)	-38.1 (± 48.67)	
Week 48	-30.0 (± 44.72)	-75.0 (± 50.0)	-50.0 (± 50.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Cushing's disease clinical signs and symptoms - Waist circumference

End point title	Percent change in Cushing's disease clinical signs and symptoms - Waist circumference
End point description:	
Clinically relevant threshold (at any time point). Reduction of ≥ 5%, Reduction of ≥ 10%	
End point type	Secondary
End point timeframe:	
Baseline, week 12, 24 and 48	

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percent change of centimeters				
arithmetic mean (standard deviation)				
Week 12	-2.0 (± 4.29)	-2.9 (± 6.70)	-2.5 (± 5.72)	
Week 24	-5.8 (± 6.28)	-3.1 (± 5.48)	-4.4 (± 5.96)	
Week 48	-5.1 (± 5.74)	-4.1 (± 5.64)	-4.6 (± 5.62)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Cushing's disease clinical signs and symptoms -

Hirsutism

End point title	Percent change in Cushing's disease clinical signs and symptoms - Hirsutism
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End point description:

Change from baseline is shown as: Percent change from baseline (BL) =((Post BL value – BL value)/ BL value)*100. Ferriman-Gallway scoring was used: 0=minimum and 36 was maximum in females only.

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	104	
Units: percent change in scores				
arithmetic mean (standard deviation)				
Week 12	-12.2 (± 24.57)	-8.2 (± 35.30)	-10.0 (± 30.00)	
Week 24	-21.2 (± 32.72)	-16.2 (± 46.99)	18.4 (± 40.79)	
Week 48	-18.2 (± 30.12)	9.6 (± 143.83)	-2.2 (± 110.20)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in growth hormone (GH) values

End point title	Percent change from baseline in growth hormone (GH) values
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	48	55	103	
Units: percent change of µg/L				
arithmetic mean (standard deviation)				
Week 12	-17.3 (± 109.89)	-20.90 (± 156.60)	-19.3 (± 137.33)	
Week 24	-22.2 (± 62.43)	-26.2 (± 105.44)	-24.4 (± 88.70)	

Week 48	23.1 (± 127.30)	-1.0 (± 134.97)	9.7 (± 130.32)	
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in insulin growth factor - 1 (IGF - 1) values

End point title	Percent change from baseline in insulin growth factor - 1 (IGF - 1) values
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, week 12, 24 and 48

End point values	Pasireotide 600 µg	Pasireotide 900 µg	All patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	48	53	101	
Units: percent change of ng/ml				
arithmetic mean (standard deviation)				
Week 12	-53.4 (± 23.66)	-57.8 (± 23.93)	-55.9 (± 23.76)	
Week 24	-49.2 (± 26.56)	-56.2 (± 26.55)	-53.1 (± 26.53)	
Week 48	-41.8 (± 35.72)	-52.1 (± 21.87)	-47.6 (± 28.71)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	600 µg bid
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Reporting group description:

600 µg bid

Reporting group title	900 µg bid
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Reporting group description:

900 µg bid

Reporting group title	All patients
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Reporting group description:

All patients

Serious adverse events	600 µg bid	900 µg bid	All patients
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 49 (26.53%)	17 / 55 (30.91%)	30 / 104 (28.85%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism venous			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			

subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Drug ineffective			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			

subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood cortisol increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase abnormal			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight increased			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 49 (4.08%)	1 / 55 (1.82%)	3 / 104 (2.88%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis necrotising			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	0 / 49 (0.00%)	3 / 55 (5.45%)	3 / 104 (2.88%)
occurrences causally related to treatment / all	0 / 0	4 / 4	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic lesion			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glucocorticoid deficiency			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperprolactinaemia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
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			
Diabetes mellitus			
subjects affected / exposed	2 / 49 (4.08%)	1 / 55 (1.82%)	3 / 104 (2.88%)
occurrences causally related to treatment / all	1 / 2	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 49 (4.08%)	0 / 55 (0.00%)	2 / 104 (1.92%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 49 (0.00%)	2 / 55 (3.64%)	2 / 104 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Type 2 diabetes mellitus			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 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	600 µg bid	900 µg bid	All patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)	54 / 55 (98.18%)	103 / 104 (99.04%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 49 (6.12%)	4 / 55 (7.27%)	7 / 104 (6.73%)
occurrences (all)	4	4	8
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 49 (8.16%)	7 / 55 (12.73%)	11 / 104 (10.58%)
occurrences (all)	4	8	12
Fatigue			
subjects affected / exposed	11 / 49 (22.45%)	12 / 55 (21.82%)	23 / 104 (22.12%)
occurrences (all)	14	13	27
Injection site erythema			
subjects affected / exposed	3 / 49 (6.12%)	2 / 55 (3.64%)	5 / 104 (4.81%)
occurrences (all)	4	2	6
Oedema peripheral			
subjects affected / exposed	9 / 49 (18.37%)	3 / 55 (5.45%)	12 / 104 (11.54%)
occurrences (all)	9	3	12
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 49 (4.08%)	3 / 55 (5.45%)	5 / 104 (4.81%)
occurrences (all)	6	4	10
Depression			
subjects affected / exposed	4 / 49 (8.16%)	3 / 55 (5.45%)	7 / 104 (6.73%)
occurrences (all)	4	3	7
Insomnia			

subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	4 / 55 (7.27%) 4	5 / 104 (4.81%) 5
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4	1 / 55 (1.82%) 4	4 / 104 (3.85%) 8
Blood cortisol decreased subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3	1 / 55 (1.82%) 1	4 / 104 (3.85%) 4
Blood glucose increased subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 6	9 / 55 (16.36%) 10	13 / 104 (12.50%) 16
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4	1 / 55 (1.82%) 1	4 / 104 (3.85%) 5
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4	4 / 55 (7.27%) 4	7 / 104 (6.73%) 8
Insulin-like growth factor decreased subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 8	5 / 55 (9.09%) 5	10 / 104 (9.62%) 13
Weight decreased subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4	2 / 55 (3.64%) 2	5 / 104 (4.81%) 6
Injury, poisoning and procedural complications			
Procedural nausea subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4	5 / 55 (9.09%) 5	8 / 104 (7.69%) 9
Procedural pain subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	3 / 55 (5.45%) 3	3 / 104 (2.88%) 3
Cardiac disorders			
Bradycardia subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 5	3 / 55 (5.45%) 4	5 / 104 (4.81%) 9
Sinus bradycardia			

subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 7	1 / 55 (1.82%) 1	5 / 104 (4.81%) 8
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 49 (12.24%)	8 / 55 (14.55%)	14 / 104 (13.46%)
occurrences (all)	8	10	18
Headache			
subjects affected / exposed	12 / 49 (24.49%)	19 / 55 (34.55%)	31 / 104 (29.81%)
occurrences (all)	16	27	43
Presyncope			
subjects affected / exposed	3 / 49 (6.12%)	1 / 55 (1.82%)	4 / 104 (3.85%)
occurrences (all)	3	1	4
Syncope			
subjects affected / exposed	3 / 49 (6.12%)	0 / 55 (0.00%)	3 / 104 (2.88%)
occurrences (all)	3	0	3
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 49 (2.04%)	3 / 55 (5.45%)	4 / 104 (3.85%)
occurrences (all)	1	3	4
Abdominal pain			
subjects affected / exposed	10 / 49 (20.41%)	9 / 55 (16.36%)	19 / 104 (18.27%)
occurrences (all)	11	10	21
Abdominal pain upper			
subjects affected / exposed	2 / 49 (4.08%)	6 / 55 (10.91%)	8 / 104 (7.69%)
occurrences (all)	3	6	9
Constipation			
subjects affected / exposed	1 / 49 (2.04%)	4 / 55 (7.27%)	5 / 104 (4.81%)
occurrences (all)	1	4	5
Diarrhoea			
subjects affected / exposed	28 / 49 (57.14%)	23 / 55 (41.82%)	51 / 104 (49.04%)
occurrences (all)	42	27	69
Dry mouth			
subjects affected / exposed	5 / 49 (10.20%)	3 / 55 (5.45%)	8 / 104 (7.69%)
occurrences (all)	5	3	8
Dyspepsia			

subjects affected / exposed	2 / 49 (4.08%)	4 / 55 (7.27%)	6 / 104 (5.77%)
occurrences (all)	2	4	6
Faeces soft			
subjects affected / exposed	4 / 49 (8.16%)	1 / 55 (1.82%)	5 / 104 (4.81%)
occurrences (all)	9	1	10
Flatulence			
subjects affected / exposed	6 / 49 (12.24%)	5 / 55 (9.09%)	11 / 104 (10.58%)
occurrences (all)	6	5	11
Frequent bowel movements			
subjects affected / exposed	3 / 49 (6.12%)	2 / 55 (3.64%)	5 / 104 (4.81%)
occurrences (all)	3	2	5
Nausea			
subjects affected / exposed	22 / 49 (44.90%)	26 / 55 (47.27%)	48 / 104 (46.15%)
occurrences (all)	29	36	65
Vomiting			
subjects affected / exposed	3 / 49 (6.12%)	7 / 55 (12.73%)	10 / 104 (9.62%)
occurrences (all)	5	7	12
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	8 / 49 (16.33%)	22 / 55 (40.00%)	30 / 104 (28.85%)
occurrences (all)	8	26	34
Hepatic steatosis			
subjects affected / exposed	1 / 49 (2.04%)	4 / 55 (7.27%)	5 / 104 (4.81%)
occurrences (all)	1	4	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 49 (8.16%)	7 / 55 (12.73%)	11 / 104 (10.58%)
occurrences (all)	4	7	11
Hyperhidrosis			
subjects affected / exposed	0 / 49 (0.00%)	3 / 55 (5.45%)	3 / 104 (2.88%)
occurrences (all)	0	3	3
Pruritus			
subjects affected / exposed	1 / 49 (2.04%)	3 / 55 (5.45%)	4 / 104 (3.85%)
occurrences (all)	1	5	6
Rash			

subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2	4 / 55 (7.27%) 4	6 / 104 (5.77%) 6
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	4 / 49 (8.16%)	1 / 55 (1.82%)	5 / 104 (4.81%)
occurrences (all)	4	1	5
Hypothyroidism			
subjects affected / exposed	3 / 49 (6.12%)	1 / 55 (1.82%)	4 / 104 (3.85%)
occurrences (all)	3	1	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 49 (4.08%)	5 / 55 (9.09%)	7 / 104 (6.73%)
occurrences (all)	2	5	7
Back pain			
subjects affected / exposed	1 / 49 (2.04%)	4 / 55 (7.27%)	5 / 104 (4.81%)
occurrences (all)	1	5	6
Muscle spasms			
subjects affected / exposed	2 / 49 (4.08%)	3 / 55 (5.45%)	5 / 104 (4.81%)
occurrences (all)	3	5	8
Myalgia			
subjects affected / exposed	3 / 49 (6.12%)	1 / 55 (1.82%)	4 / 104 (3.85%)
occurrences (all)	3	1	4
Pain in extremity			
subjects affected / exposed	5 / 49 (10.20%)	3 / 55 (5.45%)	8 / 104 (7.69%)
occurrences (all)	6	3	9
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 49 (6.12%)	2 / 55 (3.64%)	5 / 104 (4.81%)
occurrences (all)	3	2	5
Influenza			
subjects affected / exposed	1 / 49 (2.04%)	3 / 55 (5.45%)	4 / 104 (3.85%)
occurrences (all)	2	4	6
Nasopharyngitis			
subjects affected / exposed	2 / 49 (4.08%)	7 / 55 (12.73%)	9 / 104 (8.65%)
occurrences (all)	6	13	19
Upper respiratory tract infection			

subjects affected / exposed	1 / 49 (2.04%)	6 / 55 (10.91%)	7 / 104 (6.73%)
occurrences (all)	1	8	9
Urinary tract infection			
subjects affected / exposed	0 / 49 (0.00%)	4 / 55 (7.27%)	4 / 104 (3.85%)
occurrences (all)	0	7	7
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 49 (12.24%)	1 / 55 (1.82%)	7 / 104 (6.73%)
occurrences (all)	6	1	7
Diabetes mellitus			
subjects affected / exposed	9 / 49 (18.37%)	14 / 55 (25.45%)	23 / 104 (22.12%)
occurrences (all)	10	18	28
Hypercholesterolaemia			
subjects affected / exposed	1 / 49 (2.04%)	3 / 55 (5.45%)	4 / 104 (3.85%)
occurrences (all)	1	3	4
Hyperglycaemia			
subjects affected / exposed	19 / 49 (38.78%)	22 / 55 (40.00%)	41 / 104 (39.42%)
occurrences (all)	29	23	52
Hypoglycaemia			
subjects affected / exposed	4 / 49 (8.16%)	3 / 55 (5.45%)	7 / 104 (6.73%)
occurrences (all)	9	5	14
Hypokalaemia			
subjects affected / exposed	1 / 49 (2.04%)	3 / 55 (5.45%)	4 / 104 (3.85%)
occurrences (all)	1	4	5
Type 2 diabetes mellitus			
subjects affected / exposed	5 / 49 (10.20%)	3 / 55 (5.45%)	8 / 104 (7.69%)
occurrences (all)	5	3	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2011	For better standardization and quality of the laboratory results, a central laboratory for the assessment of all parameters (except urinalysis), was implemented.
16 December 2011	Additional hepatic-related safety measures were included as a result of an internal hepatic medical review of pasireotide trials
16 April 2012	Based on the recommendation from the CHMP of the EMA, the starting dose of commercial pasireotide sc was to be 600 µg bid in EU with the option to increase the dose to 900 µg bid if the disease is not controlled (i.e. 24h-mean UFC levels above the ULN) at earliest after two months of treatment provided the 600 µg bid dose is well tolerated by the patient. This change is not applicable for countries outside of the EU. The treatment duration of maximum one year per country has been extended to the latest expected approval date in all participating countries. The treatment duration of maximum one year per country has been extended to the latest expected approval date in all participating countries.
13 September 2013	Extension of washout period of mifepristone from one to four weeks in inclusion criterion #6. The use of oral contraception after the end of the study was changed to one month (from three months) based on pasireotide sc half-life of proximately 12 hours. As per recently the 2012 ADA and EASD guidelines, further guidelines on hyperglycemia monitoring and management were added. To continue to provide access to countries which have not received pasireotide approval, the protocol has been extended to 31 Dec 2015 from 31 Dec 2013. To be in compliance with the Expanded Access Program requirements, the new process of monthly AE reporting and AESI for pasireotide sc for targeted follow-up were included
13 November 2015	To continue to provide access to Brazil and South Korea, the protocol was extended to 31 Dec 2016.
31 December 2015	Monthly reporting of non-serious adverse events was removed from the protocol as it was not required for Expanded Access Programs. It was stated that an interim analysis may be performed per health authority requests or for publication purpose. All reference to medications that might lead to QT prolongation has been re-worded to state "medication with known risk of Torsades de Pointes".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported