Clinical trial results:
A randomized, double-blind study to assess the safety and efficacy of different dose levels of Pasireotide (SOM230) subcutaneous (sc) over a 6 month treatment period in patients with de novo, persistent or recurrent Cushing's disease

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2006-004111-22
Trial protocol	DK BE IT FI FR DE PT GR GB HU ES
Global end of trial date	21 May 2014
Results information	
Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification	
Sponsor protocol code	CSOM230B2305
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00434148
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	21 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to assess the efficacy of pasireotide in terms of response to pasireotide 600 µg sc bid and 900 µg sc bid independently in patients with Cushing's disease as measured by mUFC ≤ 1 x ULN after 6 months of treatment and whose dose was not increased prior to Month 6.

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	22 December 2006
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	Spain: 3
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	China: 20
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Portugal: 2

Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Mexico: 5
Worldwide total number of subjects	162
EEA total number of subjects	74

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)	157
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The actual enrollment number in the protocol section is 162. This number reflects the participants who were randomized and received at least one dose of drug.

Pre-assignment

Screening details:

A total of 165 participants were randomized, but 1 participant from the 600ug group and 2 participants from the 900ug group were not treated. Therefore, enrollment = 162. Participants who completed month 12 and did
not enter the extension phase were not counted as discontinuations.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Pasireotide 600 ug

Arm description:

At randomization, participants received 600 ug subcutaneously (sc) twice daily (bid). Participants continued at this dose until month 6 if their month 3 mean urinary free cortisol (mUFC) was <= 2 x the upper limit of normal (ULN) and the mUFC was below or equal to their baseline mUFC. Participants not meeting the mUFC criteria at month 3 were unblinded and required to increase their dose to 900ug bid on an open label basis. Participants had the option to continue in the extension phase as long as they did not meet any discontinuation criteria or until pasireotide was available commercially in their country.

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:

600 ug subcutaneous (sc) twice daily (b.i.d.)

Arm title	Pasireotide 900 ug

Arm description:

At randomization, participants received 600 ug subcutaneously (sc) twice daily (bid). Participants continued at this dose until month 6 if their month 3 mean urinary free cortisol (mUFC) was <= 2 x the upper limit of normal (ULN) and the mUFC was below or equal to their baseline mUFC. Participants not meeting the mUFC criteria at month 3 were unblinded and required to increase their dose to 1200 ug bid on an open label basis. Participants had the option to continue in the extension phase as long as they did not meet any discontinuation criteria or until pasireotode was available commercially in their country.

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:

900 ug sc b.i.d.

Number of subjects in period 1	Pasireotide 600 ug	Pasireotide 900 ug
Started	82	80
Completed month 12	39	39
Completed month 12; entered extension	26	32
Completed m. 12; did not enter extension	13	7
Completed	13	7
Not completed	69	73
Consent withdrawn by subject	15	15
Adverse event, non-fatal	18	18
Condition no longer requires study drug	1	-
Administrative problems	6	10
Lost to follow-up	-	1
Abnormal test procedure result	-	1
Lack of efficacy	25	28
Protocol deviation	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Pasireotide 600 ug
Reporting group description:	
At randomization, participants received 600 ug subcutaneously (sc) twice daily (bid). Participants continued at this dose until month 6 if their month 3 mean urinary free cortisol (mUFC) was <= 2 x the upper limit of normal (ULN) and the mUFC was below or equal to their baseline mUFC. Participants not meeting the mUFC criteria at month 3 were unblinded and required to increase their dose to 900ug bid on an open label basis. Participants had the option to continue in the extension phase as long as they did not meet any discontinuation criteria or until pasireotide was available commercially in their country.	
Reporting group title	Pasireotide 900 ug
Reporting group description:	
At randomization, participants received 600 ug subcutaneously (sc) twice daily (bid). Participants continued at this dose until month 6 if their month 3 mean urinary free cortisol (mUFC) was <= 2 x the upper limit of normal (ULN) and the mUFC was below or equal to their baseline mUFC. Participants not meeting the mUFC criteria at month 3 were unblinded and required to increase their dose to 1200 ug bid on an open label basis. Participants had the option to continue in the extension phase as long as they did not meet any discontinuation criteria or until pasireotode was available commercially in their country.	

Reporting group values	Pasireotide 600 ug	Pasireotide 900 ug	Total
Number of subjects	82	80	162
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	78	79	157
From 65-84 years	4	1	5
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	40.5	39.9	
standard deviation	± 12.97	± 10.77	-
Gender, Male/Female Units: participants			
Female	62	64	126
Male	20	16	36

End points

End points reporting groups

Reporting group title	Pasireotide 600 ug

Reporting group description:

At randomization, participants received 600 ug subcutaneously (sc) twice daily (bid). Participants continued at this dose until month 6 if their month 3 mean urinary free cortisol (mUFC) was <= 2 x the upper limit of normal (ULN) and the mUFC was below or equal to their baseline mUFC. Participants not meeting the mUFC criteria at month 3 were unblinded and required to increase their dose to 900ug bid on an open label basis. Participants had the option to continue in the extension phase as long as they did not meet any discontinuation criteria or until pasireotide was available commercially in their country.

Reporting group title	Pasireotide 900 ug

Reporting group description:

At randomization, participants received 600 ug subcutaneously (sc) twice daily (bid). Participants continued at this dose until month 6 if their month 3 mean urinary free cortisol (mUFC) was <= 2 x the upper limit of normal (ULN) and the mUFC was below or equal to their baseline mUFC. Participants not meeting the mUFC criteria at month 3 were unblinded and required to increase their dose to 1200 ug bid on an open label basis. Participants had the option to continue in the extension phase as long as they did not meet any discontinuation criteria or until pasireotode was available commercially in their country.

Primary: Number of mUFC (urinary free cortisol) responders by randomized dose group

End point title	Number of mUFC (urinary free cortisol) responders by randomized dose group[1]

End point description:

A responder in the primary efficacy analysis was a patient with a mUFC≤ULN at Month 6 and whose dose was not increased prior to Month 6.

End point type	Primary

End point timeframe:

6 months

Notes:

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

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: Responders				
number (confidence interval)	12 (7 to 22.3)	21 (16.6 to 35.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mUFC

End point title	Change from baseline in mUFC

End point description:

Twenty four hour urine samples were collected to obtain mUFC measurements. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 3 months, 12 months

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: nmol/24h				
arithmetic mean (standard deviation)				
month 3 (n=61,62)	-375.8 (± 631.07)	-343.4 (± 485.48)		
month 12 (n=37,35)	-572.6 (± 941.44)	-350.7 (± 380.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first UFC response

End point title	Time to first UFC response

End point description:

Time to first UFC response is defined as the number of months from baseline to first attainment of UFC response.

End point type	Secondary

End point timeframe:

12 months

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: months				
median (inter-quartile range (Q1-Q3))	1 (0.9 to 2.7)	1 (0.9 to 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in serum cortisol

End point title	Percent change from baseline in serum cortisol

End point description:

Blood samlpes were drawn to obtain serum cortisol levels. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 months

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: nmol/L				
arithmetic mean (standard deviation)				
month 0.5 (n=77,76)	-4 (± 28.23)	-10.8 (± 30.57)		
month 1 (n=78,72)	-7.3 (± 30.13)	-7.7 (± 32)		
month 1.5 (n=75,71)	-5.5 (± 27.65)	-7.1 (± 31.34)		
month 2 (n=73,67)	-0.7 (± 35.81)	-6.4 (± 29.75)		
month 2.5 (n=70,67)	-3.3 (± 31.4)	-10.1 (± 31.23)		
month 3 (n=70,67)	-2.6 (± 35.79)	-10.2 (± 25.6)		
month 4 (n=68,61)	-6.9 (± 31.88)	-10.8 (± 28.1)		
month 5 (n=62,58)	-4.3 (± 36.96)	-10.8 (± 26.5)		
month 6 (n=59,57)	-5.6 (± 34.28)	-9.3 (± 31.45)		
month 7 (n=52,53)	-9.8 (± 34.44)	-5.8 (± 26.35)		
month 8 (n=50,46)	-10.2 (± 30.85)	-9.9 (± 35.79)		
month 9 (n=46,48)	-5.4 (± 33.49)	-5.8 (± 31.56)		
month 10 (n=42,47)	-11.2 (± 30.25)	-9.3 (± 28.39)		
month 11 (n=41,41)	-8.2 (± 38.19)	-14 (± 29.63)		
month 12 (n=39,38)	-11.6 (± 33.75)	-15.2 (± 21.99)		
month 15 (n=26,26)	-10.5 (± 30.14)	-12.5 (± 29.27)		
month 18 (n=26,25)	-7.6 (± 40.35)	-17.8 (± 28.39)		
month 21 (n=21,25)	-12.1 (± 34.23)	-15.5 (± 34.94)		
month 24 (n=18,22)	-17.9 (± 43.46)	-18.1 (± 34.27)		
month 27 (n=16,18)	-9 (± 41.71)	-12.7 (± 28.53)		
month 30 (n=14,19)	-22.8 (± 35.43)	-22.7 (± 32.46)		
month 33 (n=13,15)	-9.5 (± 44.64)	-25.2 (± 25.96)		
month 36 (n=10,13)	-12.7 (± 65.43)	-13.3 (± 37.84)		
month 39 (n=10,12)	-26.6 (± 42.89)	-25.9 (± 33.15)		
month 42 (n=10,12)	-17.8 (± 39.54)	-18.1 (± 35.25)		

month 45 (n=10,11)	-12.5 (± 44.89)	-8.5 (± 32.55)		
month 48 (n=9,11)	-19.7 (± 37.88)	-20.1 (± 39.42)		
month 51 (n=9,9)	-17.6 (± 34.6)	-24 (± 31.53)		
month 54 (n=9,9)	-25 (± 30.49)	-6.8 (± 28.07)		
month 57 (n=8,8)	-11 (± 56.61)	-30.8 (± 22.21)		
month 60 (n=8,8)	-24.5 (± 31.89)	-18.9 (± 22.05)		
month 63 (n=6,7)	-28.6 (± 31.2)	-24 (± 26.41)		
month 66 (n=4,6)	-6.7 (± 29.29)	-22.5 (± 36.19)		
month 69 (n=3,5)	-13.4 (± 42.68)	-33.6 (± 10.31)		
month 72 (n=3,4)	-4.5 (± 40.94)	-22.7 (± 23.57)		
month 75 (n=2,3)	-63.3 (± 41.13)	-23.2 (± 25.71)		
month 78 (n=1,1)	14.5 (± 99999.99)	-53.3 (± 99999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in mean adrenocorticotropic hormone (ACTH)

End point title	Percent change from baseline in mean adrenocorticotropic hormone (ACTH)

End point description:

Blood samples were drawn to obtain ACTH levels. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 months

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: percent change				
arithmetic mean (standard deviation)				
month 0.5 (n=78,75)	9.3 (± 181.17)	-15.9 (± 30.75)		
month 1 (n=78,71)	-10 (± 37.29)	-19.1 (± 30.47)		
month 1.5 (n=74,69)	-13.4 (± 31.64)	-10.5 (± 38.05)		
month 2 (n=72,66)	-7.7 (± 40.86)	-13.2 (± 35.38)		

month 2.5 (n=69,65)	-8.2 (± 37.32)	-12 (± 47.02)		
month 3 (n=69,66)	-9.2 (± 40.85)	-16.3 (± 31.93)		
month 4 (n=66,61)	-7.2 (± 38.42)	-12.8 (± 44.06)		
month 5 (n=62,55)	-3 (± 42.5)	-15 (± 38.89)		
month 6 (n=58,55)	-8.4 (± 43.61)	-17.3 (± 35.6)		
month 7 (n=52,52)	-11.4 (± 45.25)	-14.6 (± 30.88)		
month 8 (n=48,46)	-5 (± 51.75)	-17 (± 36.87)		
month 9 (n=46,47)	-5.3 (± 55.27)	-18.2 (± 35.87)		
month 10 (n=42,46)	-10.2 (± 48.82)	-18.2 (± 34.18)		
month 11 (n=42,40)	-11.5 (± 44.52)	-17.4 (± 39.06)		
month 12 (n=39,39)	-7.4 (± 53.83)	-26.5 (± 33.38)		
month 15 (n=26,26)	-14.5 (± 43.44)	-16.3 (± 32.01)		
month 18 (n=26,25)	-5.9 (± 57.56)	-21.2 (± 32.91)		
month 21 (n=20,23)	-1.5 (± 51.52)	-17.3 (± 34.34)		
month 24 (n=18,21)	-10.9 (± 47.95)	-18 (± 26.53)		
month 27 (n=16,18)	-10.4 (± 53.33)	-12.5 (± 39.39)		
month 30 (n=14,18)	-14.7 (± 56.17)	-20 (± 40.82)		
month 33 (n=13,14)	-9.4 (± 55.01)	-2.4 (± 33.07)		
month 36 (n=10,13)	19.1 (± 112.26)	1.2 (± 35.33)		
month 39 (n=10,12)	-20.9 (± 48.68)	-5.3 (± 40.02)		
month 42 (n=10,12)	-6.7 (± 59.61)	2.7 (± 42.35)		
month 45 (n=9,11)	11.9 (± 89.59)	8.1 (± 50.09)		
month 48 (n=9,9)	-10.8 (± 65.52)	11.7 (± 55.85)		
month 51 (n=9,9)	0 (± 65.82)	-3.1 (± 48.21)		
month 54 (n=9,9)	4.6 (± 77.49)	7.3 (± 52.94)		
month 57 (n=7,7)	9.6 (± 59.86)	-5 (± 45.19)		
month 60 (n=8,8)	9.6 (± 61.38)	-1.3 (± 39.01)		
month 63 (n=6,7)	11.9 (± 73.78)	15.4 (± 50.66)		
month 66 (n=4,6)	25.3 (± 75.31)	18.3 (± 61.35)		
month 69 (n=3,5)	38.9 (± 78.34)	-1.2 (± 23.98)		
month 72 (n=3,3)	35.6 (± 78.48)	22 (± 46.15)		
month 75 (n=2,3)	-5 (± 77.78)	23.1 (± 110.92)		
month 78 (n=1,1)	50 (± 99999.99)	-11.1 (± 99999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in clinical signs and symptoms of Cushing's disease: sitting sytolic blood pressure (SBP) and sitting diastolic blood pressure (DBP)

End point title	Mean change from baseline in clinical signs and symptoms of Cushing's disease: sitting sytolic blood pressure (SBP) and sitting diastolic blood pressure (DBP)

End point description:

Sitting blood pressure assessments were performed at every study visit. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, month 3, month 6, month 12, month 24, month 36, month 48, month 60

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: mmHg				
arithmetic mean (standard deviation)				
Sitting SBP, month 3 (n=70,67)	-7.4 (± 17.37)	-9.9 (± 17.01)		
Sitting SBP, month 6 (n=59,57)	-6.8 (± 19.35)	-11.4 (± 15.92)		
Sitting SBP, month 12 (n=39,39)	-2.8 (± 18.4)	-9.4 (± 14.61)		
Sitting SBP, month 24 (n=18,23)	-11.6 (± 12.82)	-11 (± 11.58)		
Sitting SBP, month 36 (n=10,13)	-3 (± 17.08)	-11.5 (± 16.23)		
Sitting SBP, month 48 (n=9,10)	-12 (± 14.15)	-3.6 (± 14.56)		
Sitting SBP, month 60 (n=7,8)	-12.8 (± 17.1)	-2 (± 11.83)		
Sitting DBP, month 3 (n=70,67)	-3.3 (± 11.01)	-4.1 (± 13.11)		
Sitting DBP , month 6 (n=59,57)	-4.2 (± 13.54)	-5 (± 11.56)		
Sitting DBP, month 12 (n=39,39)	-2 (± 11.65)	-5.4 (± 10.86)		
Sitting DBP, month 24 (n=18,23)	-8.1 (± 11.35)	-6.4 (± 9.37)		
Sitting DBP, month 36 (n=10,13)	-6.8 (± 14.17)	-7.3 (± 8.25)		
Sitting DBP, month 48 (n=9,10)	-11.7 (± 12.02)	-1 (± 9.3)		
Sitting DBP, month 60 (n=7,8)	-9.1 (± 9.79)	0.7 (± 7.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in clinical signs and symptoms of Cushing's disease: body mass index (BMI)

End point title	Mean change from baseline in clinical signs and symptoms of Cushing's disease: body mass index (BMI)

End point description:

BMI was determined by using height and weight measurements. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, month 3, month 6, month 12, month 24, month 36, month 48 and month 60

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: kg/m^2				
arithmetic mean (standard deviation)				
month 3 (n=70,67)	-1 (± 1.26)	-1.4 (± 1.29)		
month 6 (n=59,57)	-1.2 (± 1.64)	-2.1 (± 1.72)		
month 12 (n=40,39)	-2.1 (± 2.19)	-2.8 (± 2.21)		
month 24 (n=18,23)	-3.4 (± 2.97)	-3 (± 2.67)		
month 36 (n=10,13)	-2.9 (± 2.47)	-3.3 (± 3.48)		
month 48 (n=9,10)	-3.1 (± 2.14)	-2.4 (± 2.6)		
month 60 (n=8,8)	-2.8 (± 1.85)	-2 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in clinical signs and symptoms of Cushing's disease: waist circumference

End point title	Mean change from baseline in clinical signs and symptoms of Cushing's disease: waist circumference

End point description:

Waist circumference was measured with a measuring tape correctly positioned. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, month 3, month 6, month 12, month 24, month 36, month 48, month 60

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: cm				
arithmetic mean (standard deviation)				
month 3 (n=64,66)	-1 (± 10.47)	-2.2 (± 5.23)		
month 6 (n=53,54)	-1.9 (± 8.33)	-3.4 (± 5.39)		
month 12(n=34,35)	-4.4 (± 9.4)	-5.6 (± 7.86)		

month 24 (n=17,22)	-8.7 (± 9.54)	-5.1 (± 10.22)		
month 36 (n=9,13)	-7.8 (± 10.46)	-6.4 (± 9.97)		
month 48 (n=8,10)	-8.3 (± 11.59)	-5.1 (± 10.03)		
month 60 (n=7,8)	-7.3 (± 12.08)	-4.6 (± 10.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in clinical signs and symptoms of Cushing's disease: total cholesterol and triglycerides

End point title	Mean change from baseline in clinical signs and symptoms of Cushing's disease: total cholesterol and triglycerides

End point description:

Blood samples were drawn to obtain total cholesterol and triglycerides' levels. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, month 3, month 6, month 12, month 24, month 36, month 48, month 60

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: mmol/L				
arithmetic mean (standard deviation)				
Cholesterol, month 3 (n=70,67)	-0.2 (± 1.06)	-0.3 (± 1.01)		
Cholesterol, month 6 (n=59,55)	-0.4 (± 1.24)	-0.4 (± 0.98)		
Cholesterol, month 12 (n=40,39)	-0.5 (± 1.29)	-0.6 (± 1.18)		
Cholesterol, month 24 (n=18,22)	-0.6 (± 1.39)	-0.3 (± 0.81)		
Cholesterol, month 36 (n=10,12)	-0.8 (± 1.24)	-0.1 (± 0.64)		
Cholesterol, month 48 (n=9,10)	-0.9 (± 1.63)	-0.4 (± 0.8)		
Cholesterol, month 60 (n=8,8)	-1.5 (± 1.57)	-0.4 (± 1)		
Triglycerides, month 3 (n=70,67)	0.1 (± 1.07)	0.1 (± 1.01)		
Triglycerides, month 6 (n=59,55)	0 (± 0.92)	0.1 (± 1)		
Triglycerides, month 12 (n=40,39)	-0.1 (± 0.77)	-0.2 (± 0.69)		
Triglycerides, month 24 (n=18,22)	0 (± 1.05)	0 (± 0.82)		
Triglycerides, month 36 (n=10,12)	-0.2 (± 0.99)	0.3 (± 1.38)		
Triglycerides, month 48 (n=9,10)	-0.5 (± 0.94)	0.4 (± 1.32)		
Triglycerides, month 60 (n=8,8)	-0.7 (± 1.01)	0.2 (± 1.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in clinical signs and symptoms of Cushing's disease: Beck Depression Inventory (BDI-II) score

End point title	Mean change from baseline in clinical signs and symptoms of Cushing's disease: Beck Depression Inventory (BDI-II) score

End point description:

The BDI-II is a 21 item self-report rating inventory measuring characteristic attitudes and symptoms of depression. The BDI-II contains 21 questions, each answer being scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. The scores range as follows: 0-13: minimal depression; 14-19: mild depression; 20-28: moderate depression; and 29-63: severe depression. A negative change from baseline indicates imrpovement.

End point type	Secondary

End point timeframe:

baseline, month 3, month 6, month 12, month 24, month 36, month 48, month 60

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: score on a scale				
arithmetic mean (standard deviation)				
month 3 (n=66,65)	-4.6 (± 8.29)	-1.9 (± 9.88)		
month 6 (n=56,55)	-4.6 (± 9.49)	-5.5 (± 8.81)		
month 12 (n=38,37)	-4.6 (± 9.19)	-5.2 (± 9.94)		
month 18 (n=6,6)	-1.3 (± 5.24)	-7.8 (± 5.78)		
month 24 (n=0,1)	99999.99 (± 99999.99)	-12 (± 99999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in clinical signs and symptoms of Cushing's disease: Ferriman-Galway hirsutism score

End point title	Mean change from baseline in clinical signs and symptoms of Cushing's disease: Ferriman-Galway hirsutism score

End point description:

The Ferriman Gallwey scoring system is used to score the degree of excess male pattern body hair. The scorecard of every body location under survey begins from 0 (no excessive terminal hair growth) to 4 (extensive terminal hair growth) and the numbers are added up to a maximum count of 36. A score >= 6 indicates the hirsutism. A negative change from baseline indicates imrpovement.

End point type	Secondary

End point timeframe:

baseline, month 3, month 6, month 12, month 24, month 36, month 48, month 60

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: score on a scale				
arithmetic mean (standard deviation)				
month 3 (n=52,50)	-1.3 (± 3.02)	-1.3 (± 3.46)		
month 6 (n=44,47)	-0.9 (± 2.88)	-2.4 (± 4.7)		
month 12 (n=30,35)	-1.3 (± 1.99)	-3.5 (± 4.65)		
month 24 (n=12,22)	-2.8 (± 2.72)	-4 (± 4.34)		
month 36 (n=7,12)	-3.7 (± 2.69)	-3.2 (± 4.09)		
month 48 (n=6,10)	-6 (± 3.85)	-2.5 (± 2.84)		
month 60 (n=5,8)	-5 (± 3.32)	-2.9 (± 3.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in clinical signs and symptoms of Cushing's disease: bone mineral density (BMD)

End point title	Mean change from baseline in clinical signs and symptoms of Cushing's disease: bone mineral density (BMD)

End point description:

BMD was measured using Lunar or Hologic dual-energy X-ray absorptiometry (DXA) Instruments. Measurements were done in the lumbar vertebrae (L1-L4), proximal femur (total hip) and proximal femur (femur neck). A negative change from baseline indicates imrpovement.

End point type	Secondary

End point timeframe:

baseline, month 3, month 6, month 12, month 24, month 36, month 48, month 60

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: mg/cm^3				
arithmetic mean (standard deviation)				
Lumbar vertebrae, month 3 (n=2,2)	0 (± 0.02)	0 (± 0)		
Lumbar vertebrae, month 6 (n=47,39)	0 (± 0.06)	0 (± 0.04)		
Lumbar vertebrae, month 12 (n=33,29)	0 (± 0.07)	0 (± 0.05)		
Lumbar vertebrae, month 24 (n=16,16)	0 (± 0.04)	0 (± 0.05)		
Lumbar vertebrae, month 36 (n=8,9)	0 (± 0.09)	0.1 (± 0.12)		
Lumbar vertebrae, month 48 (n=9,8)	0 (± 0.12)	0 (± 0.05)		
Lumbar vertebrae, month 60 (n=7,6)	0 (± 0.14)	0 (± 0.08)		
Proximal femur (total hip), month 3 (2,2)	0 (± 0.04)	0 (± 0.01)		
Proximal femur (total hip), month 6 (n=46,38)	0 (± 0.07)	0 (± 0.05)		
Proximal femur (total hip), month 12 (n=33,26)	0 (± 0.04)	0 (± 0.03)		

Proximal femur (total hip), month 24 (n=16,13)	0 (± 0.04)	0 (± 0.03)		
Proximal femur (total hip), month 36 (n=8,8)	0 (± 0.03)	0 (± 0.06)		
Proximal femur (total hip), month 48 (n=8,8)	0 (± 0.04)	0 (± 0.05)		
Proximal femur (total hip), month 60 (n=7,6)	-0.1 (± 0.14)	0 (± 0.06)		
Proximal femur (femur neck), month 3 (n=2,2)	0 (± 0)	0 (± 0.03)		
Proximal femur (femur neck), month 6 (n=46,38)	0 (± 0.03)	0 (± 0.05)		
Proximal femur (femur neck), month 12 (n=33,28)	0 (± 0.04)	0 (± 0.07)		
Proximal femur (femur neck), month 24 (n=16,14)	0 (± 0.05)	0 (± 0.04)		
Proximal femur (femur neck), month 36 (n=8,8)	0 (± 0.02)	0 (± 0.04)		
Proximal femur (femur neck), month 48 (n=9,7)	0 (± 0.05)	0 (± 0.04)		
Proximal femur (femur neck), month 60 (7,6)	0 (± 0.1)	0 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in clinical signs and symptoms of Cushing's disease: body composition

End point title	Mean change from baseline in clinical signs and symptoms of Cushing's disease: body composition

End point description:

Body composition as in percentage of body fat by region was assessed by total body scan. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, month 3, month 6, month 12, month 24, month 36, month 48, month 60

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: Percentage of body fat				
arithmetic mean (standard deviation)				
Month 3 (n=2,2)	2.9 (± 1.48)	0.3 (± 0.78)		
Month 6 (n=39,32)	-0.4 (± 3.77)	-0.9 (± 4.06)		
Month 12 (n=29,22)	-3 (± 4.23)	-1.6 (± 4.27)		
Month 24 (n=13,14)	-1.9 (± 3.24)	-1.9 (± 5.7)		
Month 36 (n=5,8)	-2 (± 4.2)	-1.1 (± 4.94)		
Month 48 (n=4,7)	-2 (± 5.07)	0.1 (± 5.63)		
Month 60 (n=4,6)	-2.8 (± 4.64)	-0.5 (± 4.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in tumor volume

End point title	Change from baseline in tumor volume

End point description:

Pituitary magnetic resonance imaging (MRI) was performed to determine tumor volume. A negative change from baseline indicates imrpovement.

End point type	Secondary

End point timeframe:

baseline, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78 months

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: cm^3				
arithmetic mean (standard deviation)				
month 6 (n=25, 28)	9.3 (± 44.02)	-19 (± 36.82)		
month 12 (n=15, 18)	-8.1 (± 62.17)	-43.8 (± 49.47)		
month 18 (n=8, 11)	-18.1 (± 71.62)	-36 (± 65.42)		
month 24 (n=7, 13)	-27.4 (± 82.68)	-11.5 (± 66.28)		
month 30 (n=6, 8)	-52.1 (± 55.2)	-20.9 (± 77.16)		
month 36 (n=3, 5)	-94.1 (± 10.15)	-27.6 (± 78.86)		
month 42 (n=3, 3)	-95.2 (± 8.4)	84 (± 282.6)		
month 48 (n=3, 3)	-20.5 (± 130.9)	29.2 (± 164.67)		
month 54 (n=3, 2)	-29.1 (± 107.4)	20.3 (± 170.15)		
month 60 (n=3, 2)	-13.5 (± 136.97)	127.6 (± 321.88)		
month 66 (n= 1, 1)	-100 (± 99999.99)	269.8 (± 99999.99)		
month 72 (n=1, 0)	45.6 (± 99999.99)	99999.99 (± 99999.99)		
month 78 (n=1, 0)	77.2 (± 99999.99)	99999.99 (± 99999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in health related quality of life (HRQL) score

End point title	Percentage change from baseline in health related quality of life (HRQL) score

End point description:

A Cushing's syndrome health related quality of life (HRQL) questionnaire was completed. The Cushing's Syndrome HRQL questionnaire contains 12 sentences with 5 possible answers each. The answers are based on Likert scales, with 5 response categories: Always, Often, Sometimes, Rarely and Never; or Very much, Quite a bit, Somewhat, Very little, and Not at all. The answers to each of the items are rated on a scale of 1 to 5. "1" corresponds to the response category "Always" or "Very much" and "5" corresponds to the category "Never" or "Not at all". The score is the sum of all item responses and can range from 12 to 60 points. The lower the score, the greater the Cushing's Syndrome impacts on HRQoL. A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 3 months, 6 months, 12 months

End point values	Pasireotide 600 ug	Pasireotide 900 ug		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	80		
Units: Percentage change in HRQL score				
arithmetic mean (standard deviation)				
month 3 (n=67,66)	20.7 (± 60.26)	40.1 (± 135.47)		
month 6 (n= 55,56)	19.6 (± 47.78)	52.2 (± 169.47)		
month 12 (n=20,20)	54.9 (± 95.83)	111.5 (± 266.75)		

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	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Pasireotide 600 ug bid
Reporting group description:	
Pasireotide 600 ug bid	
Reporting group title	Pasireotide 900 ug bid
Reporting group description:	
Pasireotide 900 ug bid	

Serious adverse events	Pasireotide 600 ug bid	Pasireotide 900 ug bid	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 82 (28.05%)	25 / 80 (31.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 82 (0.00%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secretory adenoma of pituitary			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			

subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 82 (1.22%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 82 (1.22%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug ineffective			
subjects affected / exposed	1 / 82 (1.22%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microlithiasis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			

subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 82 (1.22%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve paralysis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tympanic membrane perforation			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 82 (2.44%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			

subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue movement disturbance			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	2 / 82 (2.44%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	4 / 82 (4.88%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 82 (0.00%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	3 / 82 (3.66%)	3 / 80 (3.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicitis			

subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 82 (1.22%)	3 / 80 (3.75%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food intolerance			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pasireotide 600 ug bid	Pasireotide 900 ug bid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 82 (95.12%)	79 / 80 (98.75%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 82 (12.20%)	8 / 80 (10.00%)	
occurrences (all)	12	10	
Hypotension			
subjects affected / exposed	4 / 82 (4.88%)	5 / 80 (6.25%)	
occurrences (all)	9	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 82 (15.85%)	6 / 80 (7.50%)	
occurrences (all)	21	8	
Fatigue			
subjects affected / exposed	12 / 82 (14.63%)	24 / 80 (30.00%)	
occurrences (all)	14	30	
Injection site haemorrhage			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	1	5	
Injection site pain			
subjects affected / exposed	3 / 82 (3.66%)	4 / 80 (5.00%)	
occurrences (all)	3	4	
Malaise			

subjects affected / exposed	2 / 82 (2.44%)	5 / 80 (6.25%)	
occurrences (all)	3	11	
Oedema peripheral			
subjects affected / exposed	9 / 82 (10.98%)	6 / 80 (7.50%)	
occurrences (all)	9	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 82 (6.10%)	3 / 80 (3.75%)	
occurrences (all)	6	3	
Oropharyngeal pain			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	1	4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 82 (7.32%)	10 / 80 (12.50%)	
occurrences (all)	8	10	
Depression			
subjects affected / exposed	3 / 82 (3.66%)	4 / 80 (5.00%)	
occurrences (all)	3	7	
Insomnia			
subjects affected / exposed	3 / 82 (3.66%)	13 / 80 (16.25%)	
occurrences (all)	3	16	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 82 (14.63%)	6 / 80 (7.50%)	
occurrences (all)	15	8	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 82 (7.32%)	3 / 80 (3.75%)	
occurrences (all)	7	4	
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 82 (7.32%)	1 / 80 (1.25%)	
occurrences (all)	7	1	
Blood glucose increased			
subjects affected / exposed	6 / 82 (7.32%)	3 / 80 (3.75%)	
occurrences (all)	6	3	
Blood insulin decreased			

subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	2	7	
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 82 (6.10%)	7 / 80 (8.75%)	
occurrences (all)	8	7	
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 82 (13.41%)	7 / 80 (8.75%)	
occurrences (all)	13	9	
Glycosylated haemoglobin increased			
subjects affected / exposed	10 / 82 (12.20%)	8 / 80 (10.00%)	
occurrences (all)	11	9	
International normalised ratio increased			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	1	4	
Lipase increased			
subjects affected / exposed	7 / 82 (8.54%)	5 / 80 (6.25%)	
occurrences (all)	8	8	
Low density lipoprotein increased			
subjects affected / exposed	5 / 82 (6.10%)	3 / 80 (3.75%)	
occurrences (all)	9	3	
Prothrombin time prolonged			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	1	5	
Weight decreased			
subjects affected / exposed	3 / 82 (3.66%)	5 / 80 (6.25%)	
occurrences (all)	5	5	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 82 (0.00%)	4 / 80 (5.00%)	
occurrences (all)	0	4	
Procedural pain			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	1	5	
Cardiac disorders			

Sinus bradycardia subjects affected / exposed occurrences (all)	8 / 82 (9.76%) 13	2 / 80 (2.50%) 2	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	9 / 82 (10.98%) 11	9 / 80 (11.25%) 10	
Dysgeusia subjects affected / exposed occurrences (all)	3 / 82 (3.66%) 5	4 / 80 (5.00%) 5	
Headache subjects affected / exposed occurrences (all)	25 / 82 (30.49%) 66	25 / 80 (31.25%) 68	
Migraine subjects affected / exposed occurrences (all)	0 / 82 (0.00%) 0	4 / 80 (5.00%) 8	
Somnolence subjects affected / exposed occurrences (all)	2 / 82 (2.44%) 2	4 / 80 (5.00%) 4	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 82 (1.22%) 1	5 / 80 (6.25%) 7	
Iron deficiency anaemia subjects affected / exposed occurrences (all)	3 / 82 (3.66%) 3	4 / 80 (5.00%) 5	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	4 / 82 (4.88%) 5	6 / 80 (7.50%) 7	
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	3 / 82 (3.66%) 3	4 / 80 (5.00%) 5	
Gastrointestinal disorders Abdominal distension			

subjects affected / exposed	6 / 82 (7.32%)	6 / 80 (7.50%)	
occurrences (all)	10	7	
Abdominal pain			
subjects affected / exposed	19 / 82 (23.17%)	21 / 80 (26.25%)	
occurrences (all)	41	35	
Abdominal pain upper			
subjects affected / exposed	11 / 82 (13.41%)	8 / 80 (10.00%)	
occurrences (all)	15	9	
Constipation			
subjects affected / exposed	9 / 82 (10.98%)	4 / 80 (5.00%)	
occurrences (all)	9	4	
Diarrhoea			
subjects affected / exposed	49 / 82 (59.76%)	46 / 80 (57.50%)	
occurrences (all)	80	69	
Dyspepsia			
subjects affected / exposed	1 / 82 (1.22%)	5 / 80 (6.25%)	
occurrences (all)	1	6	
Faeces soft			
subjects affected / exposed	3 / 82 (3.66%)	4 / 80 (5.00%)	
occurrences (all)	3	6	
Haemorrhoids			
subjects affected / exposed	3 / 82 (3.66%)	4 / 80 (5.00%)	
occurrences (all)	3	7	
Nausea			
subjects affected / exposed	40 / 82 (48.78%)	47 / 80 (58.75%)	
occurrences (all)	53	71	
Vomiting			
subjects affected / exposed	3 / 82 (3.66%)	9 / 80 (11.25%)	
occurrences (all)	4	11	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	25 / 82 (30.49%)	25 / 80 (31.25%)	
occurrences (all)	31	29	
Skin and subcutaneous tissue disorders			
Acne			

subjects affected / exposed	5 / 82 (6.10%)	2 / 80 (2.50%)	
occurrences (all)	7	2	
Alopecia			
subjects affected / exposed	10 / 82 (12.20%)	11 / 80 (13.75%)	
occurrences (all)	10	18	
Dry skin			
subjects affected / exposed	5 / 82 (6.10%)	5 / 80 (6.25%)	
occurrences (all)	5	7	
Ecchymosis			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	1	4	
Pruritus			
subjects affected / exposed	6 / 82 (7.32%)	7 / 80 (8.75%)	
occurrences (all)	9	8	
Rash			
subjects affected / exposed	6 / 82 (7.32%)	4 / 80 (5.00%)	
occurrences (all)	10	4	
Skin exfoliation			
subjects affected / exposed	5 / 82 (6.10%)	3 / 80 (3.75%)	
occurrences (all)	7	4	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 82 (3.66%)	4 / 80 (5.00%)	
occurrences (all)	3	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 82 (7.32%)	10 / 80 (12.50%)	
occurrences (all)	15	11	
Back pain			
subjects affected / exposed	5 / 82 (6.10%)	7 / 80 (8.75%)	
occurrences (all)	5	9	
Muscle spasms			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	1	5	
Myalgia			

subjects affected / exposed	11 / 82 (13.41%)	6 / 80 (7.50%)	
occurrences (all)	30	8	
Neck pain			
subjects affected / exposed	0 / 82 (0.00%)	4 / 80 (5.00%)	
occurrences (all)	0	4	
Pain in extremity			
subjects affected / exposed	7 / 82 (8.54%)	4 / 80 (5.00%)	
occurrences (all)	8	4	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 82 (0.00%)	4 / 80 (5.00%)	
occurrences (all)	0	4	
Influenza			
subjects affected / exposed	10 / 82 (12.20%)	5 / 80 (6.25%)	
occurrences (all)	11	11	
Nasopharyngitis			
subjects affected / exposed	12 / 82 (14.63%)	12 / 80 (15.00%)	
occurrences (all)	18	17	
Upper respiratory tract infection			
subjects affected / exposed	6 / 82 (7.32%)	2 / 80 (2.50%)	
occurrences (all)	7	2	
Urinary tract infection			
subjects affected / exposed	4 / 82 (4.88%)	6 / 80 (7.50%)	
occurrences (all)	4	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 82 (9.76%)	9 / 80 (11.25%)	
occurrences (all)	9	11	
Diabetes mellitus			
subjects affected / exposed	17 / 82 (20.73%)	18 / 80 (22.50%)	
occurrences (all)	17	22	
Hypercholesterolaemia			
subjects affected / exposed	8 / 82 (9.76%)	12 / 80 (15.00%)	
occurrences (all)	11	13	
Hyperglycaemia			

subjects affected / exposed	31 / 82 (37.80%)	35 / 80 (43.75%)	
occurrences (all)	39	45	
Hyperlipidaemia			
subjects affected / exposed	5 / 82 (6.10%)	3 / 80 (3.75%)	
occurrences (all)	7	4	
Hypertriglyceridaemia			
subjects affected / exposed	6 / 82 (7.32%)	5 / 80 (6.25%)	
occurrences (all)	10	6	
Hypoglycaemia			
subjects affected / exposed	12 / 82 (14.63%)	5 / 80 (6.25%)	
occurrences (all)	17	7	
Hypokalaemia			
subjects affected / exposed	6 / 82 (7.32%)	5 / 80 (6.25%)	
occurrences (all)	6	6	
Type 2 diabetes mellitus			
subjects affected / exposed	10 / 82 (12.20%)	5 / 80 (6.25%)	
occurrences (all)	11	7	
Vitamin B12 deficiency			
subjects affected / exposed	2 / 82 (2.44%)	5 / 80 (6.25%)	
occurrences (all)	4	6	
Vitamin D deficiency			
subjects affected / exposed	5 / 82 (6.10%)	5 / 80 (6.25%)	
occurrences (all)	6	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2006	Amendment 1 was to add a protocol version number to the cover page of the original protocol and to add a section describing the history of prior protocol amendments.
15 March 2007	Amendment 2 was to add the requirement for additional gallbladder ultrasounds to be performed every three months at the German sites only.
18 April 2007	Amendment 3 was to add closer glucose monitoring for patients with diabetes or impaired fasting glucose as an additional safety measure at the French sites only.
25 May 2007	Amendment 4 was to change the criteria for dose escalation at Month 3 from mUFC > 1.5 x ULN or ≤ 50% reduction compared to baseline to mUFC < 2 x ULN. It also changed the definition of responders at Month 6 such that any patient dose escalated and unblinded at Month 3 will be automatically counted as a non-responder in the primary efficacy analysis. Other changes, including changes to the inclusion and exclusion criteria were also made.
15 June 2007	Amendment 5 was to add an analysis of injection site reactions as requested by the German health authorities as well as to specify that DXA scans were not to be performed in Germany.
10 December 2007	Amendment 6 was to lower the UFC entry criterion from ≤ 2 x ULN to ≤ 1.5 x ULN. The Month 3 dose-determination criteria were adapted as a consequence. The response criteria at Month 6 were amended from mean UFC ≤ 1.5 x ULN and a >50% reduction in mUFC to mUFC ≤ 1 x ULN. Midnight salivary cortisol measurements were added. An extension treatment phase was added for patients benefiting from study treatment. The multiple comparison procedure was removed. Several inclusion and exclusion criteria were amended including a prolongation of the exclusion of pituitary irradiation from 2 to 10 years prior to study start. Further minor changes and corrections to the protocol were also made.
19 February 2008	Amendment 8 was to include a summary paragraph on dose adjustments and discontinuation during the extension phase for easier understanding and to request additional confirmation of a pituitary ACTH source for patients without IPSS or histological confirmation upon specific request by the French authorities for the French sites only.
04 March 2008	Amendment 9 was a local amendment valid only for China to set the maximum dose a patient may receive to 900 µg b.i.d. upon specific request by the Chinese Health Authorities.
30 April 2010	Amendment 10 was issued to allow doses lower than 300 ug bid in patients who require lower doses due to tolerability issues as long as efficacy was maintained, to amend the management of hyperglycemia according to published guidelines, and to add a steering committee.
12 December 2011	Amendment 11 was issued to include additional hepatic-related safety measures as a result of an internal hepatic medical review of pasireotide studies.

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.

No statistical analysis was planned for this outcome measure.
Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Notes: