Clinical trial results:
A randomized, double-blind, multicenter, phase III study to evaluate the efficacy and safety of pasireotide LAR in patients with 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	2009-011128-70
Trial protocol	GB ES DE NL BE PL IT
Global end of trial date	21 December 2016

Results information

Result version number	v1 (current)
This version publication date	19 July 2018
First version publication date	19 July 2018

Trial information

Trial identification

Sponsor protocol code	CSOM230G2304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01374906
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	21 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of two pasireotide long-acting regimens (starting doses of 10 mg and 30 mg followed by up-titration if needed or continuation of the same dose) independently in patients with Cushing’s disease after 7 months of treatment regardless of up titration at Month 4.

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	04 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	China: 36
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Spain: 3

Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	150
EEA total number of subjects	54

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)	147
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At least 148 patients (Pts.) were planned & 150 were randomized & analyzed. Pts. were all treated with either pasireotide long-acting 10 mg or pasireotide long-acting 30 mg. 81 Pts. completed the Core phase & entered the Extension phase with 39 completing the Extension phase.

Pre-assignment

Screening details:

Planned: at least 148 patients - Randomized & Analyzed: 150 patients; 74 patients in 10 mg arm and 76 patients in 30 mg arm.

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	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	10 mg pasireotide LAR dose

Arm description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 10 mg of Pasireotide LAR.

Arm type	Experimental
Investigational medicinal product name	pasireotide LAR
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Pasireotide long-acting was administered as an intra-muscular depot intragluteal injection once every 28 days (±2 days). Pasireotide long-acting ampoules were supplied to the investigators at dose strengths of 10 mg, 10 mg + 20 mg and 40 mg kits.

Arm title	30 mg pasireotide LAR dose

Arm description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 30 mg of Pasireotide LAR.

Arm type	Experimental
Investigational medicinal product name	pasireotide LAR
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Pasireotide long-acting was administered as an intra-muscular depot intragluteal injection once every 28 days (±2 days). Pasireotide long-acting ampoules were supplied to the investigators at dose strengths of 10 mg, 10 mg + 20 mg and 40 mg kits.

Number of subjects in period 1	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose
Started	74	76
Completed	34	28
Not completed	40	48
Abnormal laboratory value(s)	-	3
Adverse event, serious fatal	-	2
Consent withdrawn by subject	15	9
Adverse event, non-fatal	10	11
Unsatisfactory therapeutic effect	11	19
Administrative problems	2	2
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	10 mg pasireotide LAR dose
Reporting group description:	
Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 10 mg of Pasireotide LAR.	
Reporting group title	30 mg pasireotide LAR dose
Reporting group description:	
Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 30 mg of Pasireotide LAR.	

Reporting group values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose	Total
Number of subjects	74	76	150
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)	73	74	147
From 65-84 years	1	2	3
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	38.3	38.6	
standard deviation	± 12.52	± 12.99	-
Gender, Male/Female Units: Subjects			
Female	58	60	118
Male	16	16	32
Race/Ethnicity Units: Subjects			
Caucasian	39	44	83
Asian	27	24	51
Black	2	0	2
Other	6	8	14

End points

End points reporting groups

Reporting group title	10 mg pasireotide LAR dose
Reporting group description:	
Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 10 mg of Pasireotide LAR.	
Reporting group title	30 mg pasireotide LAR dose
Reporting group description:	
Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 30 mg of Pasireotide LAR.	
Subject analysis set title	5 mg pasireotide LAR dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
These patients were dosed with 5 mg of Pasireotide LAR to assess Pharmacokinetics (PK).	
Subject analysis set title	40 mg pasireotide LAR dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
These patients were dosed with 40 mg of Pasireotide LAR to assess Pharmacokinetics (PK).	
Subject analysis set title	5 mg pasireptide LAR dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
These patients were dosed with 5 mg of Pasireotide LAR to assess Pharmacokinetics (PK).	
Subject analysis set title	40 mg pasireotide LAR dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
These patients were dosed with 40 mg of Pasireotide LAR to assess Pharmacokinetics (PK).	

Primary: Percentage participants that attained a mUFC ≤ 1.0 x ULN at Month 7 regardless of dose titration

End point title	Percentage participants that attained a mUFC ≤ 1.0 x ULN at Month 7 regardless of dose titration[1]
End point description:	
Percentage of participants that attained a mean urinary free cortisol (mUFC) <= 1.0 x upper limit of normal (ULN) at Month 7 regardless of dose up-titration at Month 4. Patients who discontinued before month 4 evaluations classed as non-responders. For patients missing month 7 mUFC assessments, the last available mUFC assessment at or after month 4 was carried forward as the month 7 mUFC assessment value.	
End point type	Primary
End point timeframe:	
Month 7	

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: All analyses in this study were descriptive in nature. No comparisons were made between the two arms, and no p-values are reported. For the primary and key-secondary, success was based on estimating the response rate (and 95% CI) in each arm.

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 95%)	41.9 (30.51 to 53.94)	40.8 (29.65 to 52.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants that attained a mUFC ≤ 1.0 x ULN at Month 7 and had not had a dose increase at Month 4

End point title	Percentage of participants that attained a mUFC ≤ 1.0 x ULN at Month 7 and had not had a dose increase at Month 4

End point description:

Percentage of participants that attain a mUFC ≤ 1.0×ULN at Month 7 and had not had a dose increase at Month 4. Patients who had a dose increase prior to Month 7 were counted as non-responders in this analysis. Patients who discontinued before month 4 evaluations classed as non-responders. For patients missing month 7 mUFC assessments, the last available mUFC assessment at or after month 4 was carried forward as the month 7 mUFC assessment value. A responder was defined as a patient who attains mUFC ≤1.0 X ULN and had not had a dose increase at Month 4.

End point type	Secondary

End point timeframe:

Month 7

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 95%)	28.4 (18.50 to 40.05)	31.6 (21.39 to 43.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change in mean urinary free cortisol (mUFC) from baseline

End point title	Actual change in mean urinary free cortisol (mUFC) from baseline

End point description:

Actual change in mUFC (nmol/24h) from baseline by randomized groups.

End point type	Secondary

End point timeframe:
baseline, Month 7 (M7), Month 12 (M12), Month 24 (M24) , Month 36 (M36)

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: nmol/24h				
arithmetic mean (standard deviation)				
M7 (n = 57, 67)	-192.4 (± 271.59)	-234.3 (± 362.86)		
M12 (n = 50, 54)	-195.1 (± 282.46)	-247.6 (± 387.05)		
M24 (n = 33, 25)	-236.2 (± 292.91)	-265.2 (± 313.47)		
M36 (n = 14, 4)	-398.4 (± 136.09)	-164.6 (± 66.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in mean urinary free cortisol (mUFC) from baseline

End point title	Percentage change in mean urinary free cortisol (mUFC) from baseline

End point description:
Percentage change in mUFC (nmol/24h) from baseline by randomized groups.

End point type	Secondary

End point timeframe:
M7, M12, M24, M36

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage change				
arithmetic mean (standard deviation)				
M7 (n= 57, 67)	-29.3 (± 102.76)	-33.2 (± 61.37)		
M12 (n= 50, 54)	-30.3 (± 79.73)	-31.1 (± 78.41)		
M24 (n= 33, 25	-50.9 (± 76.48)	-51.2 (± 35.41)		
M36 (n = 14, 4)	-71.6 (± 20.44)	-48.8 (± 11.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who attain mUFC ≤ 1.0 x ULN

End point title	Percentage of patients who attain mUFC ≤ 1.0 x ULN

End point description:

Controlled responder: mUFC ≤ 1.0×ULN by randomized groups.

End point type	Secondary

End point timeframe:

M7, M12, M24, M36, M48, M60

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 95%)				
M7 - Controlled responder (n = 74, 76)	39.2 (28.04 to 51.23)	40.8 (29.65 to 52.67)		
M12 - Controlled responder (n = 74, 76)	35.1 (24.39 to 47.11)	25.0 (15.77 to 36.26)		
M24 - Controlled responder (n = 63, 61)	39.7 (27.57 to 52.80)	21.3 (11.86 to 33.68)		
M36 - Controlled responder (n = 50, 50)	22.0 (11.53 to 35.96)	4.0 (0.49 to 13.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who attain mUFC ≤1.0 x ULN or have at least 50 % reduction from baseline in mUFC

End point title	Percentage of patients who attain mUFC ≤1.0 x ULN or have at least 50 % reduction from baseline in mUFC

End point description:

Controlled responder: mUFC ≤ 1.0×ULN. Partially controlled responder: at least 50% reduction in mUFC from Baseline, and mUFC >1.0×ULN.

End point type	Secondary

End point timeframe:

M7, M12, M24, M36, M48, M60

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 95%)				
M7 (n = 74, 76)	44.6 (33.02 to 56.61)	53.9 (42.13 to 65.45)		
M12 (n= 74, 76)	45.9 (34.29 to 57.93)	42.1 (30.86 to 53.98)		
M24 (n= 63, 61)	46.0 (33.39 to 59.06)	27.9 (17.15 to 40.83)		
M36 (n = 50, 50)	28.0 (16.23 to 42.49)	6.0 (1.25 to 16.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who are controlled responders (mUFC ≤ 1.0 xULN) on at least 4 of the 7 mUFC assessments by Month 7 & on at least 7 of the 12 mUFC assessments by Month 12.

End point title	Percentage of patients who are controlled responders (mUFC ≤ 1.0 xULN) on at least 4 of the 7 mUFC assessments by Month 7 & on at least 7 of the 12 mUFC assessments by Month 12.

End point description:

Percentage of patients with mUFC ≤ 1.0 x ULN at a minimum of 4 months up to and including Month 7, and at a minimum of 7 months up to and including Month 12 by randomized groups.

End point type	Secondary

End point timeframe:

Month 7, Month 12

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 95%)				
Month 7	25.7 (16.22 to 37.16)	31.6 (21.39 to 43.25)		
Month 12	25.7 (16.22 to 37.16)	25.0 (15.77 to 36.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with uncontrolled response at Month 7 & Month 12 within the subset of patients who had uncontrolled response at a) Months 1 and 2; b) Months 1, 2, and 3

End point title	Percentage of patients with uncontrolled response at Month 7 & Month 12 within the subset of patients who had uncontrolled response at a) Months 1 and 2; b) Months 1, 2, and 3

End point description:

Percentage of patients with mUFC > 1.0 xULN at Month 7 and Month 12 within the subset of patients who were uncontrolled at a) Months 1 & 2, b) Months 1, 2, & 3 by randomized groups.

End point type	Secondary

End point timeframe:

Month 7, Month12

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (not applicable)				
Uncontrolled Resp @ M7: subset: M1 & 2 (33, 33)	60.6	60.6		
Uncontrolled Resp @ M7: subset: M1,2 & 3 (31, 29)	61.3	65.5		
Uncontrolled Resp @ M12: subset: M1 & 2 (33, 33)	69.7	69.7		
Uncontrolled Resp @ M12: subset: M1 & 2 (31, 29)	74.2	72.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first achievement of attaining a mUFC ≤ 1.0 x ULN or at least a 50% reduction in mUFC from baseline

End point title	Time to first achievement of attaining a mUFC ≤ 1.0 x ULN or at least a 50% reduction in mUFC from baseline

End point description:

Time to first achievement of attaining a mUFC ≤ 1.0 x ULN or at least a 50% reduction in mUFC from baseline by randomized groups.

End point type	Secondary
End point timeframe: Momth 7, Month 12	

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage of participants				
number (confidence interval 95%)				
Month 7	86.2 (76.1 to 93.5)	83.4 (72.6 to 91.8)		
Month 12	90.1 (80.7 to 96.2)	94.5 (81.0 to 99.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of controlled or partially controlled response

End point title	Duration of controlled or partially controlled response
End point description: Duration of controlled or partially controlled response is defined as the period starting from the date of patient's first normalization (mUFC≤ 1.0 x ULN) or at least 50% reduction from baseline up to the date when the patient's mUFC >1.0 x ULN and the reduction from baseline falls to less than 50% for the first time.	
End point type	Secondary
End point timeframe: Month 6, 12, 18	

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage of participants				
number (confidence interval 95%)				
Month 6	78.0 (66.5 to 87.7)	72.9 (61.2 to 83.4)		
Month 12	84.0 (73.1 to 92.2)	82.8 (71.5 to 91.5)		
Month 18	84.0 (73.1 to 92.2)	87.1 (74.6 to 95.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline on plasma adrenocorticotropic hormone (ACTH) over time

End point title	Percentage change from baseline on plasma adrenocorticotropic hormone (ACTH) over time

End point description:

Percentage change in ACTH (pmol/L) from Baseline by randomized groups.

End point type	Secondary

End point timeframe:

Months 7, 12, 24 & 36

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage change				
arithmetic mean (standard deviation)				
M7 (n = 54, 62)	2.7 (± 57.14)	-13.5 (± 46.75)		
M12 (n = 44, 52)	-10.2 (± 57.57)	-14.5 (± 38.72)		
M24 (n = 31, 23)	-12.1 (± 43.51)	2.5 (± 68.69)		
M36 (n = 13, 5)	-15.4 (± 36.90)	-0.6 (± 48.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline on serum cortisol over time

End point title	Percentage change from baseline on serum cortisol over time

End point description:

Percentage change in serum cortisol (nmol/L) from Baseline by randomized groups.

End point type	Secondary

End point timeframe:

Months 7, 12, 24 & 36

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage change				
arithmetic mean (standard deviation)				
M7 (n = 55, 66)	-8.2 (± 37.83)	-5.1 (± 40.20)		
M12 (n = 46, 54)	-12.1 (± 29.69)	-0.4 (± 35.91)		
M24 (n = 32, 25)	-15.6 (± 30.67)	-7.4 (± 38.37)		
M36 (n = 14, 5)	0.6 (± 55.67)	-23.2 (± 31.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from baseline in clinical signs over time: Blood Pressure

End point title	Actual change from baseline in clinical signs over time: Blood Pressure

End point description:

Change in blood pressure measurements from Baseline.

End point type	Secondary

End point timeframe:

Month 7

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	67		
Units: mmHg				
arithmetic mean (standard deviation)				
Supine systolic blood pressure (SBP)	-6.8 (± 15.64)	-4.6 (± 14.51)		
Supine diastolic blood (DBP) pressure	-4.8 (± 12.06)	-3.0 (± 12.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in clinical signs over time

End point title	Percentage change from baseline in clinical signs over time

End point description:

Percentage change in parameter measurements: blood pressure, body mass index, waist circumference, fasting serum lipid profile, weight, bone density and body composition (examined by DXA scan) from

Baseline

End point type	Secondary

End point timeframe:

Month 7

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	67		
Units: Percentage change				
arithmetic mean (standard deviation)				
SBP (n = 57, 67)	-4.3 (± 11.46)	-3.0 (± 10.18)		
DBP (n = 57, 67)	-4.7 (± 14.19)	-2.6 (± 13.78)		
BMI (n = 57, 67)	-2.6 (± 5.26)	-6.1 (± 6.94)		
Weight (n = 57, 67)	-2.6 (± 5.26)	-6.1 (± 6.91)		
Waist circumference (n = 53, 63)	-1.4 (± 8.60)	-6.6 (± 10.06)		
HDL (n = 55, 64)	-6.7 (± 15.18)	0.3 (± 20.91)		
Total cholesterol (n = 56, 64)	-7.2 (± 16.86)	-6.6 (± 16.40)		
Triglycerides (n = 56, 64)	4.2 (± 39.54)	-0.9 (± 39.61)		
Body composition (n = 41, 48)	-2.4 (± 6.68)	-3.6 (± 10.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients having a favorable shift from baseline in clinical signs

End point title	Percentage of patients having a favorable shift from baseline in clinical signs

End point description:

This includes patients with improvements, no change or worsening in symptoms from baseline. Clinical signs over time include: facial rubor, fat pads, hirsutism, striae, (via photographs by a second local physician who was blinded to the treatment dose and time point of the photograph) and muscle strength.

End point type	Secondary

End point timeframe:

Month 7

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage of participants				
number (not applicable)				

Facial rubor (n = 52, 56)	32.7	53.6		
Hirsutism (females only) (n= 42,46)	22.2	32.6		
Striae (n = 52, 55)	23.1	23.6		
Bruising (n = 52, 56)	25.0	14.3		
Supraclavicular fat pad (n= 52,56)	40.4	28.6		
Dorsal fat pad (n = 52, 55)	28.8	40.0		
Muscle strength (n = 56, 66)	8.9	4.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants that attained a mean urinary free cortisol (mUFC) <= 1.0 x upper limit of normal (ULN) at Month 7 regardless of dose up-titration at Month 4.

End point title	Percentage of participants that attained a mean urinary free cortisol (mUFC) <= 1.0 x upper limit of normal (ULN) at Month 7 regardless of dose up-titration at Month 4.

End point description:

All of the participants who discontinued prior to month 4 evaluations were classed as non-responders. For participants missing month 7 mUFC assessments, the last available mUFC assessment at or after month 4 was carried forward as the month 7 mUFC assessment value. Analysis split by screening strata of mUFC Stratum 1: mUFC 1.5x to < 2.0 x ULN Stratum 2: mUFC 2.0x to <= 5.0 x ULN

End point type	Secondary

End point timeframe:

Month 7

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 95%)				
stratum:1.5 x ULN to < 2.0 x ULN (n=25,25)	52.0 (31.31 to 72.20)	52.0 (31.31 to 72.20)		
stratum:2.0 x ULN to <= 5.0 x ULN (n = 49, 51)	36.7 (23.42 to 51.71)	35.3 (22.43 to 49.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients that attain a reduction of at least 50% in mUFC from baseline

End point title	Percentage of patients that attain a reduction of at least 50% in mUFC from baseline

End point description:

All of the participants who discontinued prior to month 4 evaluations were classed as non-responders. For participants missing month 7 mUFC assessments, the last available mUFC assessment at or after month 4 was carried forward as the month 7 mUFC assessment value. Analysis split by screening strata of mUFC Stratum 1:

End point type	Secondary

End point timeframe:

Months 7, 12, 24 & 36

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 95%)				
M7	35.1 (24.39 to 47.11)	43.4 (32.08 to 55.29)		
M12	35.1 (24.39 to 47.11)	38.2 (27.25 to 50.02)		
M24 (n = 24, 14)	83.3 (62.62 to 95.26)	57.1 (28.86 to 82.34)		
M36 (n = 8, 3)	100 (63.06 to 100.00)	33.33 (0.84 to 90.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first achievement of at least a 50% reduction in mUFC from baseline

End point title	Time to first achievement of at least a 50% reduction in mUFC from baseline

End point description:

Time to first achievement of a 5by randomized groups.0% reduction in mUFC from baseline

End point type	Secondary

End point timeframe:

every month in the core phase and every 3 months in the extension phase) up to and including the cut-off date for the Month 12 CSR (10-Nov-2015)

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage of participants				
number (confidence interval 95%)				

M7	80.5 (69.7 to 89.3)	73.4 (62.4 to 83.4)		
M12	84.4 (74.0 to 92.3)	80.7 (69.4 to 89.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of at least 50% reduction in mUFC from baseline

End point title	Duration of at least 50% reduction in mUFC from baseline

End point description:

Duration of 50% reduction from baseline is defined as the period starting from the date of patient's first 50% reduction from baseline

End point type	Secondary

End point timeframe:

Months 6, 12 & 18

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Percentage of participants				
number (confidence interval 95%)				
M6	78.4 (66.6 to 88.3)	77.8 (66.0 to 87.7)		
M12	84.9 (73.7 to 93.1)	83.7 (72.6 to 92.1)		
M18	84.9 (73.7 to 93.1)	83.7 (72.6 to 92.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) parameter: Ctrough

End point title	Pharmacokinetic (PK) parameter: Ctrough

End point description:

Pasireotide trough levels (Ctrough) was one of the parameters used for PK assessments. Ctrough is the pre-dose PK concentration with an elapsed time from previous injection of 28+/-2 days. All patients randomized to the study had at least one PK observation and were therefore included in the pharmacokinetic analysis set (PAS). PK observations with missing concentrations, missing dose, missing elapsed time or an elapsed time from previous injection outside of 28 ±2 days window were excluded.

End point type	Secondary

End point timeframe:

Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose	5 mg pasireotide LAR dose	40 mg pasireotide LAR dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65	64	5	44
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 29 (n = 65, 64, 0, 0)	2.03 (± 1.25)	7.63 (± 4.58)	9.99 (± 9.99)	9.9 (± 9.99)
Day 57 (n = 57, 61, 1, 0)	2.35 (± 1.15)	7.82 (± 4.22)	0.83 (± 9.99)	9.99 (± 9.99)
Day 85 (n = 59, 51, 2, 0)	2.39 (± 1.32)	8.56 (± 4.26)	1.03 (± 0.63)	9.99 (± 9.99)
Day 113 (n = 51, 49, 3, 0)	2.40 (± 1.11)	8.31 (± 3.87)	1.29 (± 0.24)	9.99 (± 9.99)
Day 141 (n = 25, 50, 2, 20)	2.47 (± 0.94)	7.88 (± 4.00)	1.04 (± 0.68)	10.7 (± 4.91)
Day 169 (n = 29, 51, 2, 22)	2.47 (± 0.95)	8.46 (± 3.51)	2.01 (± 0.22)	12.0 (± 5.08)
Day 197 (n = 35, 44, 2, 21)	2.88 (± 1.29)	9.13 (± 4.25)	0.72 (± 0.39)	11.9 (± 5.87)
Day 225 (n = 22, 28, 3, 34)	2.68 (± 0.98)	8.57 (± 4.70)	1.19 (± 0.43)	11.3 (± 5.18)
Day 253 (n = 17, 27, 5, 33)	2.87 (± 1.57)	9.00 (± 4.93)	1.77 (± 0.88)	12.1 (± 5.21)
Day 281 (n = 13, 16, 3, 44)	3.36 (± 1.48)	8.18 (± 4.23)	1.24 (± 0.52)	11.4 (± 5.85)
Day 309 (n = 23, 19, 1, 43)	2.50 (± 0.99)	9.34 (± 5.61)	0.66 (± 9.99)	12.0 (± 4.58)
Day 337 (n = 21, 15, 3, 41)	3.07 (± 1.62)	8.90 (± 4.37)	1.91 (± 1.79)	12.6 (± 6.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) parameter: Cmax

End point title	Pharmacokinetic (PK) parameter: Cmax

End point description:

Pasireotide peak levels (Cmax) was one of the parameters used for PK assessments. Cmax is the post-dose PK concentration with an elapsed time from the previous injection of 21+/-2 days. All patients randomized to the study had at least one PK observation and were therefore included in the pharmacokinetic analysis set (PAS). Cmax PK observations ("Day 20" and "Day 104") with an elapsed time from the previous injection outside of 21+/-2 days window were excluded.

End point type	Secondary

End point timeframe:

Days 22, 106, 190

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose	5 mg pasireptide LAR dose	40 mg pasireotide LAR dose
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	67	69	3	22
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 22 (M 0.75) (n= 67, 69, 0, 0)	3.0 (± 1.50)	8.2 (± 3.99)	9.99 (± 9.99)	9.99 (± 9.99)
Day 106 (M 3.75) (n = 54, 51, 3, 0)	3.3 (± 1.92)	9.4 (± 3.72)	1.7 (± 0.42)	9.99 (± 9.99)

Day 190 (M6.75) (n = 32, 40, 2, 22)	4.0 (± 1.73)	10.0 (± 3.91)	1.4 (± 0.78)	12.1 (± 5.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change in standardized score of Cushing's disease HRQoL (CushingQOL) score from baseline

End point title	Actual change in standardized score of Cushing's disease HRQoL (CushingQOL) score from baseline

End point description:

CushingQol is a disease-specific patient-reported outcome instrument. It is a single-domain 12 item Cushing's disease quality of life instrument. The Cushing's syndrome quality of life (CushingQoL) questionnaire is a single domain questionnaire which includes 12 self-report items scored using a five point Likert scale anchored at (1=always/very much and 5=never/not at all). The patient is asked to report what they think or feel about their Cushing's syndrome and how much the illness has interfered in usual activities over the past 4 weeks. The total score is standardized on a 0-100 scale with lower scores indicating a greater impact on quality of life.

End point type	Secondary

End point timeframe:

Months 7, 12, 24 & 36

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: scores on a scale				
arithmetic mean (standard deviation)				
M7 (n = 56, 64)	5.7 (± 15.97)	7.8 (± 11.63)		
M12 (n = 47, 53)	6.4 (± 17.56)	6.8 (± 14.42)		
M24 (n = 32, 25)	5.9 (± 15.56)	8.7 (± 12.80)		
M36 (n = 13, 4)	1.4 (± 9.10)	14.6 (± 5.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change in SF-12v2 score from Baseline - Mental component summary

End point title	Actual change in SF-12v2 score from Baseline - Mental component summary

End point description:

SF-12v2 General Health Survey is a general patient reported outcome instrument over time. It is scored to provide eight health domain scores (Bodily Pain (BP), General Health (GH), Physical Functioning (PF), Role-Physical (RP), Social Functioning (SF), Role-Emotional (RE), Vitality (VT) and Mental Health (MH)).

These eight domain scores can be combined to form two summary scores reflecting overall physical and mental health: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The analyses reported here focus on PCS and MCS scores. The domain scores use a norm-based score, which standardizes the scores with respect to the mean and standard deviation of a nationally representative sample of United States (US) adults.

End point type	Secondary

End point timeframe:

Months 7, 12 & 24

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: scores on a scale				
arithmetic mean (standard deviation)				
M7 (n = 33, 37)	4.1 (± 8.81)	4.3 (± 8.05)		
M12 (n = 28, 33)	2.3 (± 9.97)	3.3 (± 8.26)		
M24 (n = 9, 5)	3.3 (± 10.43)	6.4 (± 2.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change in SF-12v2 score from Baseline - Physical component summary

End point title	Actual change in SF-12v2 score from Baseline - Physical component summary

End point description:

SF-12v2 General Health Survey is a general patient reported outcome instrument over time. It is scored to provide eight health domain scores (Bodily Pain (BP), General Health (GH), Physical Functioning (PF), Role-Physical (RP), Social Functioning (SF), Role-Emotional (RE), Vitality (VT) and Mental Health (MH)). These eight domain scores can be combined to form two summary scores reflecting overall physical and mental health: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The analyses reported here focus on PCS and MCS scores. The domain scores use a norm-based score, which standardizes the scores with respect to the mean and standard deviation of a nationally representative sample of United States (US) adults.

End point type	Secondary

End point timeframe:

Months 7, 12 & 24

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: scores on a scale				
arithmetic mean (standard deviation)				

M7 (n = 33, 37)	1.9 (± 8.50)	-0.8 (± 7.46)		
M12 (n = 28, 33)	4.9 (± 5.56)	-0.5 (± 6.73)		
M24 (n = 9, 5)	5.3 (± 4.32)	-1.1 (± 5.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from baseline in clinical signs over time: Body Mass Index (BMI)

End point title	Actual change from baseline in clinical signs over time: Body Mass Index (BMI)
End point description:	
Change in BMI measurements from Baseline.	
End point type	Secondary
End point timeframe:	
Month 7	

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	67		
Units: kg/m2				
arithmetic mean (standard deviation)	-0.7 (± 1.60)	-1.8 (± 2.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from baseline in clinical signs over time: Weight

End point title	Actual change from baseline in clinical signs over time: Weight
End point description:	
Actual change from baseline in clinical signs over time: Weight.	
End point type	Secondary
End point timeframe:	
Month 7	

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	67		
Units: kg				
arithmetic mean (standard deviation)	-1.8 (± 4.16)	-4.6 (± 5.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from baseline in clinical signs over time: Body Composition: Region

End point title	Actual change from baseline in clinical signs over time: Body Composition: Region

End point description:

Change in body composition: region measurements from Baseline.

End point type	Secondary

End point timeframe:

Month 7

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	48		
Units: percentage fat				
arithmetic mean (standard deviation)	-1.0 (± 2.64)	-1.8 (± 3.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from baseline in clinical signs over time: Waist circumference

End point title	Actual change from baseline in clinical signs over time: Waist circumference

End point description:

Change in waist circumference measurements from Baseline.

End point type	Secondary

End point timeframe:

Month 7

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	63		
Units: cm				
arithmetic mean (standard deviation)	-1.6 (± 8.47)	-7.1 (± 11.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change From Baseline in Clinical Signs Over Time: cholesterol & triglycerides

End point title	Actual Change From Baseline in Clinical Signs Over Time: cholesterol & triglycerides

End point description:

Change in parameter measurements: cholesterol & triglycerides from Baseline.

End point type	Secondary

End point timeframe:

Month 7

End point values	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	64		
Units: mmol/L				
arithmetic mean (standard deviation)				
Total cholesterol (n = 56, 64)	-0.5 (± 1.07)	-0.4 (± 1.00)		
HDL cholesterol (n = 55, 64)	-0.1 (± 0.28)	0 (± 0.32)		
Triglycerides (n = 56, 64)	0 (± 0.53)	-0.2 (± 0.64)		

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:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	10 mg pasireotide LAR dose

Reporting group description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 10 mg of Pasireotide LAR.

Reporting group title	30 mg pasireotide LAR dose

Reporting group description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 30 mg of Pasireotide LAR.

Reporting group title	All Patients

Reporting group description:

All Patients

Serious adverse events	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose	All Patients
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 74 (29.73%)	19 / 76 (25.00%)	41 / 150 (27.33%)
number of deaths (all causes)	0	2	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	1 / 74 (1.35%)	1 / 76 (1.32%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertensive crisis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 74 (0.00%)	2 / 76 (2.63%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood cortisol decreased			
subjects affected / exposed	1 / 74 (1.35%)	1 / 76 (1.32%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	1 / 1	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood cortisol increased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Stress fracture			
subjects affected / exposed	2 / 74 (2.70%)	0 / 76 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
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 failure			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Coronary artery occlusion			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anogenital dysplasia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedematous pancreatitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 74 (2.70%)	0 / 76 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 74 (2.70%)	3 / 76 (3.95%)	5 / 150 (3.33%)
occurrences causally related to treatment / all	2 / 2	2 / 3	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
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 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperadrenocorticism			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
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	2 / 74 (2.70%)	1 / 76 (1.32%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			

subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
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	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Diabetes mellitus			
subjects affected / exposed	1 / 74 (1.35%)	0 / 76 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 76 (1.32%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
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	10 mg pasireotide LAR dose	30 mg pasireotide LAR dose	All Patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 74 (98.65%)	76 / 76 (100.00%)	149 / 150 (99.33%)
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 74 (14.86%)	13 / 76 (17.11%)	24 / 150 (16.00%)
occurrences (all)	14	14	28
Hypotension			
subjects affected / exposed	4 / 74 (5.41%)	5 / 76 (6.58%)	9 / 150 (6.00%)
occurrences (all)	5	5	10
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 74 (13.51%)	5 / 76 (6.58%)	15 / 150 (10.00%)
occurrences (all)	11	9	20
Fatigue			
subjects affected / exposed	13 / 74 (17.57%)	15 / 76 (19.74%)	28 / 150 (18.67%)
occurrences (all)	15	18	33
Oedema peripheral			
subjects affected / exposed	9 / 74 (12.16%)	12 / 76 (15.79%)	21 / 150 (14.00%)
occurrences (all)	15	13	28
Pyrexia			
subjects affected / exposed	5 / 74 (6.76%)	2 / 76 (2.63%)	7 / 150 (4.67%)
occurrences (all)	6	2	8
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	2 / 74 (2.70%)	4 / 76 (5.26%)	6 / 150 (4.00%)
occurrences (all)	2	4	6
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 74 (10.81%)	5 / 76 (6.58%)	13 / 150 (8.67%)
occurrences (all)	8	5	13
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 74 (8.11%)	5 / 76 (6.58%)	11 / 150 (7.33%)
occurrences (all)	10	6	16
Blood cortisol decreased			
subjects affected / exposed	4 / 74 (5.41%)	2 / 76 (2.63%)	6 / 150 (4.00%)
occurrences (all)	4	5	9
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 74 (1.35%)	6 / 76 (7.89%)	7 / 150 (4.67%)
occurrences (all)	1	6	7
Blood glucose increased			
subjects affected / exposed	6 / 74 (8.11%)	7 / 76 (9.21%)	13 / 150 (8.67%)
occurrences (all)	7	7	14
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 74 (9.46%)	6 / 76 (7.89%)	13 / 150 (8.67%)
occurrences (all)	10	6	16
Glycosylated haemoglobin increased			
subjects affected / exposed	4 / 74 (5.41%)	4 / 76 (5.26%)	8 / 150 (5.33%)
occurrences (all)	5	4	9
Lipase increased			
subjects affected / exposed	2 / 74 (2.70%)	4 / 76 (5.26%)	6 / 150 (4.00%)
occurrences (all)	2	5	7
Weight decreased			
subjects affected / exposed	4 / 74 (5.41%)	3 / 76 (3.95%)	7 / 150 (4.67%)
occurrences (all)	4	3	7
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	4 / 74 (5.41%)	1 / 76 (1.32%)	5 / 150 (3.33%)
occurrences (all)	4	1	5
Cardiac disorders			
Palpitations			
subjects affected / exposed	4 / 74 (5.41%)	3 / 76 (3.95%)	7 / 150 (4.67%)
occurrences (all)	4	3	7
Sinus bradycardia			
subjects affected / exposed	4 / 74 (5.41%)	5 / 76 (6.58%)	9 / 150 (6.00%)
occurrences (all)	8	8	16
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 74 (13.51%)	8 / 76 (10.53%)	18 / 150 (12.00%)
occurrences (all)	19	9	28
Headache			
subjects affected / exposed	18 / 74 (24.32%)	10 / 76 (13.16%)	28 / 150 (18.67%)
occurrences (all)	25	14	39
Paraesthesia			
subjects affected / exposed	1 / 74 (1.35%)	4 / 76 (5.26%)	5 / 150 (3.33%)
occurrences (all)	1	5	6
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 74 (5.41%)	5 / 76 (6.58%)	9 / 150 (6.00%)
occurrences (all)	7	13	20
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	5 / 74 (6.76%)	0 / 76 (0.00%)	5 / 150 (3.33%)
occurrences (all)	6	0	6
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 74 (5.41%)	2 / 76 (2.63%)	6 / 150 (4.00%)
occurrences (all)	5	2	7
Abdominal distension			
subjects affected / exposed	4 / 74 (5.41%)	5 / 76 (6.58%)	9 / 150 (6.00%)
occurrences (all)	4	6	10
Abdominal pain			
subjects affected / exposed	11 / 74 (14.86%)	13 / 76 (17.11%)	24 / 150 (16.00%)
occurrences (all)	15	15	30

Abdominal pain upper			
subjects affected / exposed	3 / 74 (4.05%)	8 / 76 (10.53%)	11 / 150 (7.33%)
occurrences (all)	4	9	13
Constipation			
subjects affected / exposed	5 / 74 (6.76%)	5 / 76 (6.58%)	10 / 150 (6.67%)
occurrences (all)	5	5	10
Diarrhoea			
subjects affected / exposed	26 / 74 (35.14%)	35 / 76 (46.05%)	61 / 150 (40.67%)
occurrences (all)	49	67	116
Dry mouth			
subjects affected / exposed	4 / 74 (5.41%)	1 / 76 (1.32%)	5 / 150 (3.33%)
occurrences (all)	6	1	7
Flatulence			
subjects affected / exposed	3 / 74 (4.05%)	5 / 76 (6.58%)	8 / 150 (5.33%)
occurrences (all)	4	5	9
Frequent bowel movements			
subjects affected / exposed	4 / 74 (5.41%)	0 / 76 (0.00%)	4 / 150 (2.67%)
occurrences (all)	4	0	4
Nausea			
subjects affected / exposed	17 / 74 (22.97%)	16 / 76 (21.05%)	33 / 150 (22.00%)
occurrences (all)	33	21	54
Vomiting			
subjects affected / exposed	7 / 74 (9.46%)	2 / 76 (2.63%)	9 / 150 (6.00%)
occurrences (all)	11	2	13
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	15 / 74 (20.27%)	33 / 76 (43.42%)	48 / 150 (32.00%)
occurrences (all)	18	42	60
Cholestasis			
subjects affected / exposed	4 / 74 (5.41%)	2 / 76 (2.63%)	6 / 150 (4.00%)
occurrences (all)	4	2	6
Gallbladder cholesterolosis			
subjects affected / exposed	2 / 74 (2.70%)	4 / 76 (5.26%)	6 / 150 (4.00%)
occurrences (all)	2	4	6
Hepatic function abnormal			

subjects affected / exposed	2 / 74 (2.70%)	4 / 76 (5.26%)	6 / 150 (4.00%)
occurrences (all)	1	4	5
Hepatic steatosis			
subjects affected / exposed	1 / 74 (1.35%)	6 / 76 (7.89%)	7 / 150 (4.67%)
occurrences (all)	1	6	7
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 74 (2.70%)	5 / 76 (6.58%)	7 / 150 (4.67%)
occurrences (all)	2	5	7
Dry skin			
subjects affected / exposed	2 / 74 (2.70%)	5 / 76 (6.58%)	7 / 150 (4.67%)
occurrences (all)	2	5	7
Erythema			
subjects affected / exposed	2 / 74 (2.70%)	4 / 76 (5.26%)	6 / 150 (4.00%)
occurrences (all)	2	5	7
Pruritus			
subjects affected / exposed	5 / 74 (6.76%)	6 / 76 (7.89%)	11 / 150 (7.33%)
occurrences (all)	7	7	14
Rash			
subjects affected / exposed	4 / 74 (5.41%)	2 / 76 (2.63%)	6 / 150 (4.00%)
occurrences (all)	7	2	9
Skin exfoliation			
subjects affected / exposed	3 / 74 (4.05%)	4 / 76 (5.26%)	7 / 150 (4.67%)
occurrences (all)	4	4	8
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	4 / 74 (5.41%)	6 / 76 (7.89%)	10 / 150 (6.67%)
occurrences (all)	30	7	37
Hypothyroidism			
subjects affected / exposed	1 / 74 (1.35%)	4 / 76 (5.26%)	5 / 150 (3.33%)
occurrences (all)	1	4	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 74 (12.16%)	4 / 76 (5.26%)	13 / 150 (8.67%)
occurrences (all)	14	4	18
Back pain			

subjects affected / exposed	8 / 74 (10.81%)	8 / 76 (10.53%)	16 / 150 (10.67%)
occurrences (all)	12	8	20
Muscle spasms			
subjects affected / exposed	1 / 74 (1.35%)	5 / 76 (6.58%)	6 / 150 (4.00%)
occurrences (all)	1	6	7
Musculoskeletal chest pain			
subjects affected / exposed	0 / 74 (0.00%)	4 / 76 (5.26%)	4 / 150 (2.67%)
occurrences (all)	0	4	4
Myalgia			
subjects affected / exposed	4 / 74 (5.41%)	4 / 76 (5.26%)	8 / 150 (5.33%)
occurrences (all)	4	4	8
Pain in extremity			
subjects affected / exposed	6 / 74 (8.11%)	6 / 76 (7.89%)	12 / 150 (8.00%)
occurrences (all)	7	9	16
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 74 (6.76%)	2 / 76 (2.63%)	7 / 150 (4.67%)
occurrences (all)	5	4	9
Gastroenteritis			
subjects affected / exposed	7 / 74 (9.46%)	2 / 76 (2.63%)	9 / 150 (6.00%)
occurrences (all)	9	2	11
Influenza			
subjects affected / exposed	12 / 74 (16.22%)	6 / 76 (7.89%)	18 / 150 (12.00%)
occurrences (all)	14	8	22
Nasopharyngitis			
subjects affected / exposed	18 / 74 (24.32%)	13 / 76 (17.11%)	31 / 150 (20.67%)
occurrences (all)	26	26	52
Upper respiratory tract infection			
subjects affected / exposed	5 / 74 (6.76%)	6 / 76 (7.89%)	11 / 150 (7.33%)
occurrences (all)	6	7	13
Urinary tract infection			
subjects affected / exposed	10 / 74 (13.51%)	9 / 76 (11.84%)	19 / 150 (12.67%)
occurrences (all)	13	16	29
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	3 / 74 (4.05%)	12 / 76 (15.79%)	15 / 150 (10.00%)
occurrences (all)	3	13	16
Diabetes mellitus			
subjects affected / exposed	15 / 74 (20.27%)	20 / 76 (26.32%)	35 / 150 (23.33%)
occurrences (all)	15	22	37
Hypercholesterolaemia			
subjects affected / exposed	3 / 74 (4.05%)	6 / 76 (7.89%)	9 / 150 (6.00%)
occurrences (all)	3	6	9
Hyperglycaemia			
subjects affected / exposed	36 / 74 (48.65%)	35 / 76 (46.05%)	71 / 150 (47.33%)
occurrences (all)	58	53	111
Hyperlipidaemia			
subjects affected / exposed	1 / 74 (1.35%)	4 / 76 (5.26%)	5 / 150 (3.33%)
occurrences (all)	1	4	5
Hyperuricaemia			
subjects affected / exposed	5 / 74 (6.76%)	5 / 76 (6.58%)	10 / 150 (6.67%)
occurrences (all)	5	5	10
Hypoglycaemia			
subjects affected / exposed	10 / 74 (13.51%)	12 / 76 (15.79%)	22 / 150 (14.67%)
occurrences (all)	26	58	84
Type 2 diabetes mellitus			
subjects affected / exposed	3 / 74 (4.05%)	4 / 76 (5.26%)	7 / 150 (4.67%)
occurrences (all)	3	5	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2011	In the original protocol, the investigators were unblinded to the dose and mUFC value after the patient completed Month 7. This amendment extended the blind of the Investigator until the Month 12 analyses have been performed to prevent bias associated with unblinding of Investigators, and to protect the integrity of the study; the time from the start of each individual 24-hour urine collection by the patient until storage was reduced from 14 days to 6 days to take into account the stability period of urinary creatinine at normal refrigeration temperatures; to ensure the blind was maintained, explicit language was added to prevent sites from assessing any cortisol-related parameters; the exclusion criterion relating to patients with HbA1c >8% was modified to exclude such patients regardless of the use of anti-diabetic medication; exclusion criteria were modified to include hypomagnesemia as a risk factor for torsade de pointes; new process for eligibility confirmation within the IRT system was established; requirement to record salivary cortisol and mUFC on eCRFs for screen failures was removed. Data record was done via central laboratory data transfer; mifepristone washout was added and 24h creatine clearance was removed; inconsistent language was corrected throughout the protocol; editorial and typographical errors were corrected throughout the study.
13 December 2011	Additional hepatic-related safety measures as a result of an internal hepatic medical review of pasireotide studies were included; the Beck's Depression Inventory II was removed from the secondary efficacy assessments as it was no longer deemed feasible; the washout period for octreotide LAR, lanreotide SR and lanreotide autogel was clarified to be 14 weeks; in order to prevent unblinding of investigators to dose levels, the instructions for use of the pasireotide long-acting 5 mg ampoule were updated; clarification was provided through edited text and inconsistent language was corrected throughout the protocol
08 October 2012	Investigators were given the option to allow patients to remain on the current dose at Months 4, 7 and/or 9 visits in case of tolerability issues that in his/her clinical judgment would guide against a potential dose up-titration; language on glucose monitoring and treatment was expanded to reinforce glycemic goals of treatment per current ADA and European Association for the Study of Diabetes guidelines and to emphasize the need to initiate anti-hyperglycemic treatment accordingly; continued measuring quality of life change and Global impression of change over time into the extension phase allowed. In addition, a new SF-12v2 General Health Survey was introduced; pregnancy guidelines were updated; clarification was provided through edited text and inconsistent language was corrected throughout the protocol
13 May 2013	Investigators, site staff, Novartis study team and related vendors gained access to mUFC and other cortisol-related assessments throughout the study while maintaining the blinding to the randomized treatment group until the Month 12 analysis. In addition, central MRI readings were also made available to investigators, site staff, Novartis study team and related vendors throughout the study; removal of clinical benefit question pertaining to dose up-titration at Months 7, 9, 12 and during the extension phase; language related to CRH test stimulation was updated; option to roll over patients post extension phase into a long term safety study was clarified; clarification was provided through edited text, and inconsistent language was corrected throughout the protocol
29 August 2013	Instructions for use were updated for 30 mg dose using 60 mg kit and include procedure for preparation of the 30 mg dose using the 60 mg vial; patients who had completed Month 24 prior to the Month 12 database lock were allowed to continue beyond Month 24, and until the long-term safety study is opened to patients enrolled in the study; additional pregnancy assessments (urine pregnancy test) were added in the study as a safety precaution

07 June 2016	The purpose of this amendment was to clarify that DXA and MRI scans, required once every six months during treatment, were not required at the End of Study Treatment Visit if previous scan(s) were performed within the last six months. The clinical rationale for this action was that clinically relevant changes in parameters measured by these techniques were not expected to occur or be detected within a six month period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

All analyses in this study were descriptive in nature. No comparisons were made between the two arms, and no p-values are reported. For the primary and key-secondary, success was based on estimating the response rate (and 95% CI) in each arm.

Notes: