Clinical trial results:
A Phase II trial to assess the efficacy and safety of pasireotide s.c. alone or in
combination with cabergoline in patients with Cushing's disease

Summary

EudraCT number	2013-002170-49
Trial protocol	DE IT ES BE HU GR NL FR
Global end of trial date	04 September 2019

Results information

Result version number	v1 (current)
This version publication date	13 September 2020
First version publication date	13 September 2020

Trial information

Trial identification

Sponsor protocol code	CSOM230B2411

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01915303
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	04 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 September 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall efficacy of the treatment regimen of pasireotide alone or in combination with cabergoline in patients with Cushing’s disease (CD)

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	06 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Netherlands: 3
Worldwide total number of subjects	68
EEA total number of subjects	24

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)	64
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

How many patients were screened

Period 1

Period 1 title	Core Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All patients

Arm description:

Pasireotide montherapy (0.6 mg bid to 0.9 mg bid) was administered until the biochemical control was achieved and if not achieved, a combination was administered: pasireotide (0.9 mg bid) + cabergoline (0.5 QD to 1 mg QD). Patients were able to add cabergoline at anytime during core and extension

Arm type	Experimental
Investigational medicinal product name	pasireotide +/- cabergoline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

pasireotide = 0.3 mg (bid, QD in case of good response), 0.6 mg (bid), and 0.9 mg (bid) and cabergoline = 0.5 mg (QD) or 1.0 mg (QD) In case of lack of tolerability, it can be reduced: 0.5 mg (QOD) or 1.0 mg (QOD)

Number of subjects in period 1	All patients
Started	68
Completed	52
Not completed	16
Adverse event, serious fatal	2
Consent withdrawn by subject	1
Abnormal lab value	1
Adverse event, non-fatal	7
Unsatisfactory therapeutic effect	3
Protocol deviation	2

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All patients

Arm description:

Pasireotide montherapy (0.6 mg bid to 0.9 mg bid) was administered until the biochemical control was achieved and if not achieved, a combination was administered: pasireotide (0.9 mg bid) + cabergoline (0.5 QD to 1 mg QD). Patients were able to add cabergoline at anytime during core and extension

Arm type	Experimental
Investigational medicinal product name	pasireotide +/- cabergoline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Subcutaneous use, Oral use

Dosage and administration details:

pasireotide = 0.3 mg (bid, QD in case of good response), 0.6 mg (bid), and 0.9 mg (bid) and cabergoline = 0.5 mg (QD) or 1.0 mg (QD) In case of lack of tolerability, it can be reduced: 0.5 mg (QOD) or 1.0 mg (QOD)

Number of subjects in period 2[1]	All patients
Started	29
Completed	12
Not completed	17
Adverse event, serious fatal	1
Consent withdrawn by subject	4
Adverse event, non-fatal	3
Unsatisfactory therapeutic effect	8
Protocol deviation	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: All patients did not enter the extension

Baseline characteristics

Reporting groups	
Reporting group title	All patients
Reporting group description:	
Pasireotide montherapy (0.6 mg bid to 0.9 mg bid) was administered until the biochemical control was achieved and if not achieved, a combination was administered: pasireotide (0.9 mg bid) + cabergoline (0.5 QD to 1 mg QD). Patients were able to add cabergoline at anytime during core and extension	

Reporting group values	All patients	Total	
Number of subjects	68	68	
Age Categorical Units: participants			
< 65 years	64	64	
≥ 65 years	4	4	
Sex: Female, Male Units:			
Female	60	60	
Male	8	8	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	44	44	
Asian	9	9	
Native American	5	5	
Black	2	2	
Other	8	8	
Cushing's disease status			
De novo = newly diagnosed and persistent/recurrent = xxxxxxxx			
Units: Subjects			
De novo	10	10	
Persistent/recurrent	58	58	
Clinical symptoms of facial rubor			
Clinical symptoms of CD for facial rubor by severity			
Units: Subjects			
None	10	10	
Mild	17	17	
Moderate	11	11	
Severe	4	4	
Not done	26	26	
Clinical symptoms of hirsutism			
Clinical symptoms of CD for hirsutism by severity			
Units: Subjects			
None	13	13	
Mild	12	12	
Moderate	7	7	
Severe	3	3	
Not done	33	33	
Clinical symptoms of striae			
Clinical symptoms of CD for striae by severity			

Units: Subjects			
None	20	20	
Mild	10	10	
Moderate	4	4	
Severe	8	8	
Not done	26	26	
Clinical symptoms of supraclavicular fat pad			
Clinical symptoms of CD for supraclavicular fat pad by severity			
Units: Subjects			
None	8	8	
Mild	17	17	
Moderate	13	13	
Severe	4	4	
Not done	26	26	
Clinical symptoms of dorsal fat pad			
Clinical symptoms of CD for dorsal fat pad severity			
Units: Subjects			
None	3	3	
Mild	19	19	
Moderate	14	14	
Severe	6	6	
Not done	26	26	

End points

End points reporting groups

Reporting group title	All patients
Reporting group description:	
Pasireotide montherapy (0.6 mg bid to 0.9 mg bid) was administered until the biochemical control was achieved and if not achieved, a combination was administered: pasireotide (0.9 mg bid) + cabergoline (0.5 QD to 1 mg QD). Patients were able to add cabergoline at anytime during core and extension	
Reporting group title	All patients
Reporting group description:	
Pasireotide montherapy (0.6 mg bid to 0.9 mg bid) was administered until the biochemical control was achieved and if not achieved, a combination was administered: pasireotide (0.9 mg bid) + cabergoline (0.5 QD to 1 mg QD). Patients were able to add cabergoline at anytime during core and extension	

Primary: Percentage of responders with mean urinary free cortisol (mUFC) ≤ 1.0xULN collected or imputed at week 35

End point title	Percentage of responders with mean urinary free cortisol (mUFC) ≤ 1.0xULN collected or imputed at week 35[1]
End point description:	
Participants who attained mUFC ≤ 1.0 x ULN (upper limit of normal) with pasireotide alone or in combination with cabergoline. The 24h-UFC concentration results from three samples, collected during the screening period, were averaged to obtain the Baseline urinary free cortisol level. mean 24h-UFC was determined from two 24-hour urine collections collected on two consecutive days that occurred before the visit. Imputation: subjects who completed the end of treatment visit at Week 35, but had missing evaluation of mean urinary free cortisol (mUFC). The last available mUFC assessment at or after previous visit (week) before last week was carried forward as the last week mUFC assessment.	
End point type	Primary
End point timeframe:	
Baseline up to week 35	
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: Not analyzed	

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: percentage of responders				
number (confidence interval 95%)	50.0 (37.6 to 62.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean urinary free cortisol (mUFC) at scheduled visits

End point title	Mean urinary free cortisol (mUFC) at scheduled visits
End point description:	
Mean value of mUFC at each scheduled visit was determined from two 24-hour urine collections collected on two consecutive days that occurred before the visit when UFC was measured.	

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 8 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: nmol/24h				
arithmetic mean (standard deviation)				
Baseline	501.6 (± 488.66)			
Core Week 2 n-8	217.0 (± 100.69)			
Core Week 4 n=59	242.1 (± 203.47)			
Core Week 8 n=58	230.0 (± 195.21)			
Core Week 13 n=51	231.0 (± 240.98)			
Core Week 17 n=57	310.3 (± 429.64)			
Core Week 22 n=50	214.0 (± 202.80)			
Core Week 26 n=54	211.6 (± 173.58)			
Core Week 31 n=46	154.3 (± 104.16)			
Core Week 35 n=45	184.8 (± 140.13)			
Ext Week 43 n=22	136.1 (± 91.13)			
Ext Week 51 n=20	156.8 (± 108.91)			
Ext Week 59 n=24	157.7 (± 111.63)			
Ext Week 67 n=17	213.8 (± 194.99)			
Ext Week 75 n=18	157.6 (± 166.28)			
Ext Week 83 n=20	157.9 (± 134.98)			
Ext Week 91 n=18	180.0 (± 302.36)			
Ext Week 99 n=13	222.5 (± 375.67)			
Ext Week 107 n=12	118.5 (± 122.01)			
Ext Week 115 n=13	126.0 (± 80.09)			
Ext Week 123 n=13	147.5 (± 157.77)			
Ext Week 131 n=11	76.4 (± 49.92)			
Ext Week 139 n=9	92.9 (± 73.18)			
Ext Week 147 n=9	90.1 (± 55.31)			
Ext Week 155 n=4	76.3 (± 39.05)			

Ext Week 163 n=6	141.1 (± 142.42)			
Ext Week 171 n=6	89.5 (± 61.87)			
Ext Week 179 n=4	61.3 (± 43.06)			
Ext Week 187 n=4	89.9 (± 52.44)			
Ext Week 195 n=3	46.1 (± 40.21)			
Ext Week 203 n=4	194.0 (± 259.15)			
Ext Week 211 n=3	107.3 (± 37.68)			
Ext Week 219 n=2	70.6 (± 46.74)			
Ext Week 227 n=2	47.1 (± 7.99)			
Ext Week 235 n=3	62.0 (± 23.83)			
Ext Week 243 n=1	117.7 (± 9999.9)			
Ext Week 251 n=1	202.9 (± 9999.9)			
Ext Week 267 n=1	249.0 (± 9999.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of responders with mean Urinary Free Cortisol (mUFC) ≤ 1.0xULN

End point title	Percentage of responders with mean Urinary Free Cortisol (mUFC) ≤ 1.0xULN

End point description:

Actual mean value of mUFC at each scheduled visit was determined from two 24-hour urine collections collected on two consecutive days that occurred before the visit when UFC was measured.

End point type	Secondary

End point timeframe:

Baseline up to week 235

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: percentage of responders				
number (confidence interval 95%)				
Baseline	4.4 (0.9 to 12.4)			
Core Week 17 n=57	28.1 (17.0 to 41.5)			
Core Week 35 n=45	48.9 (33.7 to 64.2)			
Ext Week 43 n=22	63.6 (40.7 to 82.8)			
Ext Week 67 n=17	47.1 (23.0 to 72.2)			

Ext Week 91 n=18	61.1 (35.7 to 82.7)			
Ext Week 115 n=13	76.9 (46.2 to 95.0)			
Ext Week 139 n=9	77.8 (40.0 to 97.2)			
Ext Week 163 n=6	66.7 (22.3 to 95.7)			
Ext Week 187 n=4	75.0 (19.4 to 99.4)			
Ext Week 211 n=3	66.7 (9.4 to 99.2)			
Ext Week 235 n=3	100 (29.2 to 100.0)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Actual mean value of mUFC at each scheduled visit was determined from two 24-hour urine collections collected on two consecutive days that occurred before the visit when UFC was measured.

End point type	Secondary

End point timeframe:

Baseline up to week 235

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: percentage of responders				
number (confidence interval 95%)				
Baseline	4.4 (0.9 to 12.4)			
Core Week 17 n=57	54.4 (40.7 to 67.6)			
Core Week 35 n=45	68.9 (53.4 to 81.8)			
Ext Week 43 n=22	86.4 (65.1 to 97.1)			
Ext Week 67 n=17	76.5 (50.1 to 93.2)			
Ext Week 91 n=18	83.3 (58.6 to 96.4)			
Ext Week 115 n=13	92.3 (64.0 to 99.8)			
Ext Week 139 n=9	77.8 (40.0 to 97.2)			

Ext Week 163 n=6	83.3 (35.9 to 99.6)			
Ext Week 187 n=4	100 (39.8 to 100.0)			
Ext Week 211 n=3	66.7 (9.4 to 99.2)			
Ext Week 235 n=3	100 (29.2 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration (weeks) of controlled or partially controlled response

End point title	Duration (weeks) 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% from the first time

End point type	Secondary

End point timeframe:

from the date patient's first normalization (mUFC ≤ 1.0xULN) or at least 50% reduction from baseline up to the date when the patient's mUFC > 1.0 x ULN

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: weeks				
median (confidence interval 95%)				
Core n=36	13.1 (9.3 to 22.4)			
Extension n=20	22.0 (8.1 to 70.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma adrenocorticotropic hormone (ACTH)

End point title	Plasma adrenocorticotropic hormone (ACTH)

End point description:

A pre-dose blood draw for plasma ACTH sampling was taken at visits. Samples were analyzed by a central laboratory.

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 8 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: pmol/L				
arithmetic mean (standard deviation)				
Baseline	16.3 (± 16.3)			
Core Week 2 n-62	12.4 (± 9.91)			
Core Week 4 n=63	14.2 (± 12.50)			
Core Week 8 n=61	13.3 (± 11.90)			
Core Week 13 n=53	11.9 (± 10.98)			
Core Week 17 n=58	12.3 (± 9.03)			
Core Week 22 n=49	13.7 (± 13.82)			
Core Week 26 n=55	12.4 (± 12.09)			
Core Week 31 n=49	12.1 (± 11.02)			
Core Week 35 n=40	11.0 (± 8.71)			
Ext Week 43 n=23	11.5 (± 8.12)			
Ext Week 51 n=21	10.4 (± 6.80)			
Ext Week 59 n=23	10.7 (± 6.89)			
Ext Week 67 n=22	11.0 (± 7.23)			
Ext Week 75 n=22	9.1 (± 4.16)			
Ext Week 83 n=19	9.8 (± 8.20)			
Ext Week 91 n=19	10.6 (± 8.34)			
Ext Week 99 n=16	11.3 (± 8.50)			
Ext Week 107 n=13	9.3 (± 6.61)			
Ext Week 115 n=15	9.5 (± 7.22)			
Ext Week 123 n=14	10.6 (± 8.24)			
Ext Week 131 n=12	8.2 (± 6.01)			
Ext Week 139 n=10	10.0 (± 7.01)			
Ext Week 147 n=9	10.4 (± 7.02)			
Ext Week 155 n=9	10.4 (± 7.02)			
Ext Week 163 n=5	10.0 (± 4.85)			
Ext Week 171 n=5	7.4 (± 3.36)			
Ext Week 179 n=5	7.0 (± 3.32)			
Ext Week 187 n=5	8.6 (± 5.32)			
Ext Week 195 n=4	9.0 (± 4.76)			
Ext Week 203 n=4	8.0 (± 2.94)			
Ext Week 211 n=3	11.0 (± 4.58)			
Ext Week 219 n=2	6.0 (± 0.00)			
Ext Week 227 n=2	7.0 (± 1.41)			
Ext Week 235 n=3	10.3 (± 3.21)			
Ext Week 243 n=1	6.0 (± 9999.9)			
Ext Week 251 n=1	7.0 (± 9999.9)			
Ext Week 267 n=1	4.0 (± 9999.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum cortisol levels

End point title	Serum cortisol levels

End point description:

A pre-dose blood draw for an 8 am fasting serum cortisol measurement will be taken at visits. Samples were analyzed by a central laboratory.

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 8 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: nmol/L				
arithmetic mean (standard deviation)				
Baseline	738.6 (± 332.53)			
Core Week 2 n-62	626.1 (± 281.57)			
Core Week 4 n=64	663.6 (± 292.38)			
Core Week 8 n=61	649.0 (± 297.11)			
Core Week 13 n=53	628.8 (± 269.43)			
Core Week 17 n=58	683.0 (± 282.28)			
Core Week 22 n=49	625.4 (± 216.29)			
Core Week 26 n=55	632.7 (± 278.75)			
Core Week 31 n=49	597.5 (± 247.60)			
Core Week 35 n=40	538.2 (± 205.40)			
Ext Week 43 n=23	525.5 (± 178.63)			
Ext Week 51 n=21	512.2 (± 243.59)			
Ext Week 59 n=21	547.5 (± 193.67)			
Ext Week 67 n=22	495.4 (± 213.03)			
Ext Week 75 n=21	458.5 (± 170.88)			
Ext Week 83 n=19	419.5 (± 141.26)			
Ext Week 91 n=19	501.2 (± 235.89)			
Ext Week 99 n=16	470.9 (± 248.0)			

Ext Week 107 n=13	463.4 (± 189.27)			
Ext Week 115 n=15	501.7 (± 212.27)			
Ext Week 123 n=14	441.6 (± 150.98)			
Ext Week 131 n=12	413.8 (± 325.5)			
Ext Week 139 n=10	404.0 (± 90.87)			
Ext Week 147 n=10	585.4 (± 216.92)			
Ext Week 155 n=8	472.5 (± 122.96)			
Ext Week 163 n=6	617.0 (± 212.11)			
Ext Week 171 n=5	648.6 (± 243.79)			
Ext Week 179 n=5	599.0 (± 388.78)			
Ext Week 187 n=5	609.8 (± 292.85)			
Ext Week 195 n=4	418.8 (± 138.69)			
Ext Week 203 n=4	514.0 (± 212.27)			
Ext Week 211 n=3	551.3 (± 339.87)			
Ext Week 219 n=2	482.0 (± 25.46)			
Ext Week 227 n=2	324.5 (± 177.48)			
Ext Week 235 n=3	384.7 (± 165.17)			
Ext Week 243 n=1	679.0 (± 9999.9)			
Ext Week 251 n=1	574.0 (± 9999.9)			
Ext Week 267 n=1	638.0 (± 9999.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sitting systolic blood pressure at week 35

End point title	Sitting systolic blood pressure at week 35

End point description:

The mean arterial blood pressure determinations were obtained in the sitting position. Three measurements were taken with 5 minute intervals and the mean was used for study specific procedures

End point type	Secondary

End point timeframe:

Baseline and week 35

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	125.9 (± 14.3)			
Week 35 n=41	119.5 (± 18.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sitting diastolic blood pressure at week 35

End point title	Sitting diastolic blood pressure at week 35

End point description:

The mean arterial blood pressure determinations were obtained in the sitting position. Three measurements were taken with 5 minute intervals and the mean was used for study specific procedures

End point type	Secondary

End point timeframe:

Baseline and week 35

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	81.8 (± 9.12)			
Week 35 n=41	77.2 (± 12.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Body weight at baseline and week 35

End point title	Body weight at baseline and week 35

End point description:

Weight was was one of the measures of clinical symptoms of CD

End point type	Secondary

End point timeframe:

Baseline and week 35

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: kg				
arithmetic mean (standard deviation)				
Baseline	82.2 (± 19.1)			
Week 35 n=41	75.6 (± 20.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Body mass index at week 35

End point title	Body mass index at week 35

End point description:

Body mass index was one of the measurements of clinical symptoms of CD. Body mass index=weight in kg divided by the square of the body height (in meters)

End point type	Secondary

End point timeframe:

Baseline and week 35

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: kg/m2				
arithmetic mean (standard deviation)				
Baseline	31.3 (± 6.6)			
Week 35 n=41	28.4 (± 6.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Waist circumference at week 35

End point title	Waist circumference at week 35

End point description:

Waist circumference was one of the measurements of clinical signs of CD

End point type	Secondary

End point timeframe:

Baseline and week 35

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: cm				
arithmetic mean (standard deviation)				
Baseline	104.1 (± 19.1)			
Week 35 n=41	99.1 (± 18.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: LDL, HDL and total cholesterol at week 35

End point title	LDL, HDL and total cholesterol at week 35

End point description:

LDL=Low density lipoprotein, HDL=high density llipoprotein and total protein were analyzed by a central laboratory

End point type	Secondary

End point timeframe:

Baseline and week 35

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: mmol/L				
arithmetic mean (standard deviation)				
HDL Baseline	1.5 (± 0.3)			
HDL Week 35 n=41	1.5 (± 0.4)			
LDL Baseline	3.2 (± 1.0)			
LDL Week 35 n=41	2.8 (± 1.0)			
Total Baseline	69.4 (± 3.7)			
Total Week 35 n=41	68.6 (± 4.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean scores for Cushing QoL standardized score at week 17 and 35

End point title	Mean scores for Cushing QoL standardized score at week 17 and 35

End point description:

Patients who completed nine or more items for the 12-item Cushing's syndrome QoL questionaire were considered evaluable for that assessment. Raw scores were obtained for the 12 items using the following scoring: 1) always or very much, 2) often or quite a bit, 3) sometimes or somewhat, 4) rarely or very little, 5) never or not at all. Then the standardized score, Y, was calculated for each patient as follows: Y = 100* (X – n) / n*5 – n*1) = 100 * (X – n) / 4*n where X denoted the raw score and n the number of questions answered by the patient. The higher the score, the better the QoL. The best possible standardized score was 100 and the worst possible standardized score was 0

End point type	Secondary

End point timeframe:

Baseline and week 17 and 35

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline Mean	41.6 (± 20.2)			
Week 17 n=54	46.3 (± 19.7)			
Week 35 n=40	47.6 (± 20.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean scores of SF-12v2 domain scores at week 17 and 35

End point title	Mean scores of SF-12v2 domain scores at week 17 and 35

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. These are the scores on the original scale which have not been transformed in any way. The possible range of scores is 0 to 100, with higher scores representing better outcomes.

End point type	Secondary

End point timeframe:

Baseline, week 17 and 35

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline Bodily pain scale	42.9 (± 11.93)			
Week 17 n=52 Bodily pain scale	45.1 (± 10.75)			
Week 35 n=40 Bodily pain scale	44.9 (± 10.79)			
Baseline n=67 General health scale:	38.9 (± 9.23)			
Week 17 n=52 General health scale:	40.9 (± 8.52)			
Week 35 n=40 General health scale:	40.7 (± 8.94)			
Baseline n=67 Mental component	42.4 (± 10.17)			
Week 17 n=52 Mental component	41.9 (± 9.68)			
Week 35 n=40 Mental component	42.1 (± 8.32)			
Baseline n=67 Mental health	41.9 (± 10.48)			
Week 17 n=52 Mental health	43.0 (± 9.54)			
Week 35 n=40 Mental health	42.4 (± 8.44)			
Baseline n=67 Physical component summary	42.7 (± 9.03)			
Week 17 n=52 Physical component summary	44.0 (± 8.52)			
Week 35 n=40 Physical component summary	43.4 (± 9.59)			
Baseline n=67 Physical functioning	42.1 (± 10.17)			
Week 17 n=52 Physical functioning	41.9 (± 8.93)			
Week 35 n=40 Physical functioning	42.1 (± 11.10)			
Baseline n=67 Role emotional	39.7 (± 11.67)			
Week 17 n=52 Role emotional	38.0 (± 9.95)			
Week 35 n=40 Role emotional	38.7 (± 10.70)			
Baseline n=67 Role physical scale:	42.3 (± 10.45)			
Week 17 n=52 Role physical scale:	42.8 (± 8.73)			
Week 35 n=40 Role physical scale:	41.3 (± 9.63)			
Baseline n=67 Social functioning	42.2 (± 11.22)			
Week 17 n=52 Social functioning	43.0 (± 8.70)			
Week 35 n=40 Social functioning	43.3 (± 9.66)			
Baseline n=67 Vitality scale:	47.2 (± 10.02)			
Week 17 n=52 Vitality scale:	45.7 (± 10.29)			
Week 35 n=40 Vitality scale:	45.6 (± 8.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Facial rubor

End point title	Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Facial rubor

End point description:

Clinical symptoms include: facial rubor, hirsutism, striae, and supraclavicular and dorsal fat pad. Two photographs, one frontal and one lateral from the shoulders up were taken to assess facial plethora, supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in

standing position were taken to assess striae, and hirsutism. The photographs were assessed by a qualified physician at the site. Improvement=decrease in severity of symptom since baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 16 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: participants				
Core Week 1 n=40	5			
Core Week 2 n=37	8			
Core Week 4 n=38	8			
Core Week 8 n=37	12			
Core Week 13 n=32	11			
Core Week 17 n=32	11			
Core Week 22 n=28	10			
Core Week 26 n=31	14			
Core Week 31 n=32	15			
Core Week 35 n=26	13			
Ext Week 43 n=11	2			
Ext Week 59 n=11	3			
Ext Week 75 n=12	3			
Ext Week 91 n=10	3			
Ext Week 107 n=9	3			
Ext Week 123 n=10	2			
Ext Week 139 n=7	2			
Ext Week 155 n=4	0			
Ext Week 171 n=3	0			
Ext Week 187 n=3	0			
Ext Week 203 n=4	0			
Ext Week 219 n=2	0			
Ext Week 235 n=3	0			
Ext Week 251 n=1	0			
Ext Week 267 n=1	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Hirsutism

End point title	Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Hirsutism

End point description:

Clinical symptoms include: facial rubor, hirsutism, striae, and supraclavicular and dorsal fat pad. Two photographs, one frontal and one lateral from the shoulders up were taken to assess facial plethora,

supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position were taken to assess striae, and hirsutism. The photographs were assessed by a qualified physician at the site. Improvement=decrease in severity of symptom since baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 16 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: participants				
Core Week 1 n=35	5			
Core Week 2 n-33	3			
Core Week 4 n=32	4			
Core Week 8 n=32	4			
Core Week 13 n=27	4			
Core Week 17 n=28	3			
Core Week 22 n=25	5			
Core Week 26 n=27	8			
Core Week 31 n=28	9			
Core Week 35 n=23	7			
Ext Week 43 n=10	2			
Ext Week 59 n=9	2			
Ext Week 75 n=10	3			
Ext Week 91 n=9	2			
Ext Week 107 n=8	1			
Ext Week 123 n=9	2			
Ext Week 139 n=7	2			
Ext Week 155 n=4	2			
Ext Week 171 n=4	2			
Ext Week 187 n=3	2			
Ext Week 203 n=4	2			
Ext Week 219 n=2	1			
Ext Week 235 n=3	1			
Ext Week 251 n=1	0			
Ext Week 267 n=1	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Striae

End point title	Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Striae

End point description:

Clinical symptoms include: facial rubor, hirsutism, striae, and supraclavicular and dorsal fat pad. Two

photographs, one frontal and one lateral from the shoulders up were taken to assess facial plethora, supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position were taken to assess striae, and hirsutism. The photographs were assessed by a qualified physician at the site. Improvement=decrease in severity of symptom since baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 16 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: participants				
Core Week 1 n=40	5			
Core Week 2 n-37	2			
Core Week 4 n=38	5			
Core Week 8 n=37	8			
Core Week 13 n=32	7			
Core Week 17 n=32	7			
Core Week 22 n=28	7			
Core Week 26 n=31	9			
Core Week 31 n=32	12			
Core Week 35 n=26	8			
Ext Week 43 n11=	1			
Ext Week 59 n=11	1			
Ext Week 75 n=12	1			
Ext Week 91 n=10	1			
Ext Week 107 n=9	0			
Ext Week 123 n=10	0			
Ext Week 139 n=7	0			
Ext Week 155 n=4	1			
Ext Week 171 n=3	0			
Ext Week 187 n=3	0			
Ext Week 203 n=4	1			
Ext Week 219 n=2	0			
Ext Week 235 n=3	1			
Ext Week 251 n=1	0			
Ext Week 267 n=1	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Supraclavicular fat pad

End point title	Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Supraclavicular fat pad

End point description:

Clinical symptoms include: facial rubor, hirsutism, striae, and supraclavicular and dorsal fat pad. Two photographs, one frontal and one lateral from the shoulders up were taken to assess facial plethora, supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position were taken to assess striae, and hirsutism. The photographs were assessed by a qualified physician at the site. Improvement=decrease in severity of symptom since baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 8 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: participants				
Core Week 1 n=40	6			
Core Week 2 n-37	7			
Core Week 4 n=37	6			
Core Week 8 n=37	8			
Core Week 13 n=32	8			
Core Week 17 n=32	9			
Core Week 22 n=28	9			
Core Week 26 n=31	10			
Core Week 31 n=32	12			
Core Week 35 n=26	11			
Ext Week 43 n=11	1			
Ext Week 59 n=11	0			
Ext Week 75 n=12	1			
Ext Week 91 n=10	1			
Ext Week 107 n=9	0			
Ext Week 123 n=10	1			
Ext Week 139 n=7	1			
Ext Week 155 n=4	1			
Ext Week 171 n=3	1			
Ext Week 187 n=3	1			
Ext Week 203 n=4	1			
Ext Week 219 n=2	1			
Ext Week 235 n=3	2			
Ext Week 251 n=1	0			
Ext Week 267 n=1	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Dorsal fat pad

End point title	Number of participants with improvement in clinical symptom of hypercortisolism from baseline - Dorsal fat pad

End point description:

Clinical symptoms include: facial rubor, hirsutism, striae, and supraclavicular and dorsal fat pad. Two photographs, one frontal and one lateral from the shoulders up were taken to assess facial plethora, supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position were taken to assess striae, and hirsutism. The photographs were assessed by a qualified physician at the site. Improvement=decrease in severity of symptom since baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 16 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: participants				
Core Week 1 n=40	6			
Core Week 2 n-37	4			
Core Week 4 n=37	5			
Core Week 8 n=37	5			
Core Week 13 n=32	4			
Core Week 17 n=32	8			
Core Week 22 n=28	8			
Core Week 26 n=31	12			
Core Week 31 n=32	13			
Core Week 35 n=26	9			
Ext Week 43 n=11	3			
Ext Week 59 n=10	4			
Ext Week 75 n=12	5			
Ext Week 91 n=10	3			
Ext Week 107 n=9	2			
Ext Week 123 n=10	3			
Ext Week 139 n=7	3			
Ext Week 155 n=4	1			
Ext Week 171 n=3	1			
Ext Week 187 n=3	2			
Ext Week 203 n=4	1			
Ext Week 219 n=2	1			
Ext Week 235 n=3	2			
Ext Week 251 n=1	0			
Ext Week 267 n=1	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with shift from mild to severe in clinical signs of hypercortisolism

End point title	Number of participants with shift from mild to severe in clinical signs of hypercortisolism

End point description:

Facial rubor, hirsutism, striae, and supraclavicular and dorsal fat pad. Two photographs, one frontal and one lateral from the shoulders up will be taken to assess facial plethora,
supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position will be taken to assess striae, and hirsutism. The photographs must be assessed by a qualified physician at the site. Improvement=decrease in severity of symptom since baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 2, 4, every 4 or 5 weeks during core, every 8 weeks during extension

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: participants				
Core Week 1 Hirsutism baseline n=12	1			
Core Week 2 Hirsutism baseline n=12	1			
Core Week 4 Facial rubor baseline n=17	1			
Core Week 35 Facial rubor baseline n=17	1			
Core Week 43 Facial rubor baseline n=17	1			
Core Week 59 Facial rubor baseline n=17	1			
Core Week 59 Striae baseline n=10	1			
Core Week 67 Facial rubor baseline n=17	1			
Core Week 83 Facial rubor baseline n=17	1			
Core Week 91 Facial rubor baseline n=17	1			
Core Week 99 Facial rubor baseline n=17	1			
Core Week 99 Striae baseline n=10	1			
Core Week 99 Supraclavicular fat pad BL n=17	1			
Ext Week 107 Facial rubor baseline n=17	1			
Ext Week 107 Striae baseline n=10	1			
Core Week 107 Supraclavicular fat pad BL n=17	1			
Ext Week 115 Facial rubor baseline n=17	1			
Ext Week 115 Striae baseline n=10	1			
Ext Week 123 Facial rubor baseline n=17	1			
Ext Week 123 Striae baseline n=10	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with shift from standing easily to not being able to stand

End point title	Number of patients with shift from standing easily to not being able to stand

End point description:

To test proximal muscle strength patients should be placed in a low seated position (for instance on an examination room stool). They should be asked to extend the arms in front of them. From this seated position patients will be asked to stand up. Patients will be evaluated
using the following scale:
3. – completely unable to stand
2. – able to stand only by using arms as assistance
1. – able to stand after several efforts without using arms as assistance
0. – able to stand easily with arms extended

End point type	Secondary

End point timeframe:

Baseline up to week 267

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: participants				
Core Week 26	1			
Core Week 35	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	All Patients core@and extension phase
Reporting group description:	
All Patients core@and extension phase	

Serious adverse events	All Patients core@and extension phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 68 (22.06%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour benign			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Shock haemorrhagic			

subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Death				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Hip fracture				

subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle rupture				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery disease				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Headache				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				

Anaemia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intra-abdominal haematoma			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Glucocorticoid deficiency			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Patients core@and extension phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 68 (98.53%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	7		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 68 (10.29%)		
occurrences (all)	11		
Fatigue			
subjects affected / exposed	13 / 68 (19.12%)		
occurrences (all)	13		
Oedema peripheral			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Psychiatric disorders			
Depression			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	8		
Insomnia			
subjects affected / exposed	7 / 68 (10.29%)		
occurrences (all)	7		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	5		
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 68 (16.18%)		
occurrences (all)	11		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Mitral valve incompetence			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 68 (27.94%)		
occurrences (all)	23		
Headache			
subjects affected / exposed	20 / 68 (29.41%)		
occurrences (all)	25		
Somnolence			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	5		
Tremor			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 68 (16.18%)		
occurrences (all)	12		
Abdominal pain upper			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	6		

Diarrhoea subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	30 / 68 (44.12%) 40 4 / 68 (5.88%) 5 35 / 68 (51.47%) 43 4 / 68 (5.88%) 4		
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all) Hepatic steatosis subjects affected / exposed occurrences (all)	22 / 68 (32.35%) 25 4 / 68 (5.88%) 4		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 10 9 / 68 (13.24%) 10 8 / 68 (11.76%) 9		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all)	13 / 68 (19.12%) 14 4 / 68 (5.88%) 4		

Musculoskeletal pain subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 6		
Myalgia subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 6		
Pain in extremity subjects affected / exposed occurrences (all)	9 / 68 (13.24%) 9		
Infections and infestations Influenza subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 5		
Nasopharyngitis subjects affected / exposed occurrences (all)	11 / 68 (16.18%) 12		
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 6		
Diabetes mellitus subjects affected / exposed occurrences (all)	12 / 68 (17.65%) 14		
Glucose tolerance impaired subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 5		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		
Hyperglycaemia subjects affected / exposed occurrences (all)	35 / 68 (51.47%) 46		
Hypertriglyceridaemia			

subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	6		
Hyperuricaemia			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	6		
Hypoglycaemia			
subjects affected / exposed	11 / 68 (16.18%)		
occurrences (all)	45		
Vitamin B12 deficiency			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Vitamin D deficiency			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2014	• To add a criterion to exclude pregnant or nursing (lactating) women; • It was clarified that Dostinex (a generic form of cabergoline) would be used for the trial in available participating countries
24 July 2015	•To combine group 1 (pasireotide naïve subjects) and group 2 (subjects currently treated with maximal tolerated doses of pasireotide monotherapy) into a single cohort of subjects; • To reduce the target number of enrolled subjects (reduced from 128 to 64); • The duration of screening period was increased from 21 days to 28 days; • To change the lowest dose of pasireotide allowed for the trial (previous dose 0.3 mg bid; new dose: 0.3 mg QD). • The PK analysis was not performed as a result of combining group 1 and group 2 into one single group.
25 July 2016	At the time of this protocol amendment, pasireotide was not yet approved for commercial use and/or reimbursed in several participating countries. In order to continue to provide access to treatment for subjects in these countries and to collect longer-term safety and efficacy data, the maximum duration of the extension phase of the study was extended by two further years. The new enddate for the extension phase is 31-Dec-2017; Addition of one section "Adverse events of special interest"
12 July 2017	At the time of this protocol amendment, pasireotide was not yet approved for commercial use and/or reimbursed in several participating countries. In order to continue to provide access to treatment for subjects in these countries and to collect longer-term safety and efficacy data, the maximum duration of the extension phase of the study was extended by two further years. The new end date for the extension phase is 31-Dec-2019.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported