Clinical trial results:
An Open Label Study to Assess the Safety and Efficacy of COR-003 (2S, 4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome (CS)

Summary

EudraCT number	2013-002133-37
Trial protocol	GB ES BE NL SE DK DE IT BG CZ HU
Global end of trial date	20 November 2018

Results information

Result version number	v1 (current)
This version publication date	13 May 2021
First version publication date	13 May 2021
Summary attachment (see zip file)	Efficacy and Safety of levoketoconazole (Fleseriu et al-Efficacy &Safety of levoketoconazole in CS-TLDE2019-PRINT.pdf) Efficacy and Safety of Levoketoconazole Suppl data (Fleseriu et al-Efficacy &Safety of levoketoconazole in CS-TLDE2019-Appendix.pdf) Levoketoconazole improves clinical signs and symptoms (Geer_Pituitary_2020.pdf) Levoketoconazole in the Treatment of CS with Diabetes (fendo-12-595894.pdf) Levoketoconazole in the Treatment of Diabetes suppl table (supplemental table.docx)

Trial information

Trial identification

Sponsor protocol code	COR-2012-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01838551
WHO universal trial number (UTN)	-
Other trial identifiers	COR202101: SONICS

Notes:

Sponsors

Sponsor organisation name	Cortendo AB
Sponsor organisation address	900 Northbrook Drive, Suite 200, Trevose, United States, 19053
Public contact	Clinical Trial Information, Cortendo AB, +1 609878179, info@cortendo.com
Scientific contact	Clinical Trial Information, Cortendo AB, +1 609878179, info@cortendo.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2018
Global end of trial reached?	Yes
Global end of trial date	20 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical responder rate, defined as the proportion of subjects with normal UFC after 6 months of treatment with COR-003 in the Maintenance Phase without dose increase, and to evaluate the range of effective doses in subjects with various levels of hypercortisolism.

Protection of trial subjects:

Withdrawal criteria defined for events relating to QT interval prolongation and laboratory abnormalities related to liver tests.

Background therapy:

None defined

Evidence for comparator:

No comparators used.

Actual start date of recruitment	30 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 20

Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	Turkey: 3
Worldwide total number of subjects	94
EEA total number of subjects	52

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)	89
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 201 patients were screened between 30 July 2014 and 30 June 2017. Of these, 107 patients were screening failures, predominantly because they did not meet eligibility criteria.

Period 1

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

Arms

Arm title	Levoketoconazole Titration Phase

Arm description:

The initial dose was levoketoconazole 150 mg BID (300 mg/day), taken as 1 tablet in the morning and 1 tablet in the evening. During the first 2 to 21 weeks, dose was titrated in protocol-defined increments up to each subject's therapeutic dose, based on the subject's urinary free cortisol (UFC) levels and safety/tolerability. The interval between upward dose adjustments was to be approximately 18 days. The lowest allowed dose was 150 mg/day for subjects who could not tolerate 150 mg BID; the highest allowed dose was 600 mg BID (1200 mg/day).
The therapeutic dose had been reached when mean UFC levels (determined from a total of 4 24-h urine collections) were ≤ULN of the assay, or the maximum allowed dose (600 mg BID) had been reached, or a clinically meaningful partial response and the maximal tolerated dose had been reached.

Arm type	Experimental
Investigational medicinal product name	Levoketoconazole
Investigational medicinal product code	COR-003
Other name	2S,4R-ketoconazole
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The initial dose was levoketoconazole 150 mg BID (300 mg/day), taken as 1 tablet in the morning and 1 tablet in the evening. During the first 2 to 21 weeks, dose was titrated in protocol-defined increments up to each subject's therapeutic dose, based on the subject's UFC levels and safety/tolerability. The interval between upward dose adjustments was to be approximately 18 days. The lowest allowed dose was 150 mg/day for subjects who could not tolerate 150 mg BID; the highest allowed dose was 600 mg BID (1200 mg/day).
The therapeutic dose had been reached when mean UFC levels (determined from a total of 4 24-h urine collections) were ≤ULN of the assay, or the maximum allowed dose (600 mg BID) had been reached, or a clinically meaningful partial response and the maximal tolerated dose had been reached.

Number of subjects in period 1	Levoketoconazole Titration Phase
Started	94
Completed	77
Not completed	17
Consent withdrawn by subject	4
Physician decision	1
Adverse event, non-fatal	6

Not further specified	3
Lack of efficacy	3

Period 2

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

Arms

Arm title	Levoketoconazole Maintenance Phase

Arm description:

Dosing was to be continued for 6 months at the therapeutic dose established by dose titration in the Titration Phase. During the Maintenance Phase, levoketoconazole dose was not to be changed unless medically necessary.

Arm type	Experimental
Investigational medicinal product name	Levoketoconazole
Investigational medicinal product code	COR-003
Other name	2S,4R-ketoconazole
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing was to be continued for 6 months at the therapeutic dose established by dose titration in the Titration Phase. The required number of tablets was to be taken in the morning and evening following a protocol defined dosing scheme.

Number of subjects in period 2	Levoketoconazole Maintenance Phase
Started	77
Completed	61
Not completed	16
Consent withdrawn by subject	4
Physician decision	1
Adverse event, non-fatal	6
Not otherwise specified	1
Lack of efficacy	4

Period 3

Period 3 title	Extended Evaluation Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Levoketoconazole Extended Evaluation Phase

Arm description:

During the Extended Evaluation Phase, levoketoconazole dosing was to continue as in the Maintenance Phase. Dosing was to be continued for 6 months. The levoketoconazole dose was not to be changed unless medically necessary.

Arm type	Experimental
Investigational medicinal product name	Levoketoconazole
Investigational medicinal product code	COR-003
Other name	2S,4R-ketoconazole
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing was to be continued as in the Maintenance Phase. The required number of tablets was to be taken in the morning and evening following a protocol defined dosing scheme.

Number of subjects in period 3[1]	Levoketoconazole Extended Evaluation Phase
Started	60
Completed	46
Not completed	14
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Physician decision	2
Adverse event, non-fatal	4
Not otherwise specified	2
Lack of efficacy	3

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 but one continued into the Extended Evaluation Phase while one patient chose not to continue.

Baseline characteristics

Reporting groups	
Reporting group title	Titration Phase

Reporting group description: -

Reporting group values	Titration Phase	Total	
Number of subjects	94	94	
Age categorical Units: Subjects			
Adults (18-64 years)	89	89	
From 65-84 years	5	5	
Age continuous Units: years			
arithmetic mean	43.7		
standard deviation	± 13.4	-	
Gender categorical Units: Subjects			
Female	77	77	
Male	17	17	
Biological cause Units: Subjects			
Cushing's disease	80	80	
Ectopic ACTH secretion	1	1	
Adrenal dependent	8	8	
Unknown	5	5	
Body weight Units: kg			
arithmetic mean	84.0		
standard deviation	± 23.4	-	
Body mass index Units: kg/m2			
arithmetic mean	30.8		
standard deviation	± 8.2	-	
Time since diagnosis Units: months			
arithmetic mean	68.0		
standard deviation	± 80.4	-	
Baseline mUFC molar concentration Units: nmol/24 h			
arithmetic mean	671.4		
standard deviation	± 743.1	-	
Baseline mUFC mass concentration Units: ug/24 h			
arithmetic mean	243.3		
standard deviation	± 269.3	-	
Baseline mUFC x ULN Units: Multiples of ULN			
arithmetic mean	4.9		

standard deviation	± 5.4	-	

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received at least 1 dose of levoketoconazole. This population is used for the evaluation of efficacy and all safety analyses.

Subject analysis set title	ITT2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Identical to ITT

Reporting group values	ITT	ITT2	
Number of subjects	94	94	
Age categorical Units: Subjects			
Adults (18-64 years)	89		
From 65-84 years	5		
Age continuous Units: years			
arithmetic mean	43.7		
standard deviation	± 13.5	±	
Gender categorical Units: Subjects			
Female	77		
Male	17		
Biological cause Units: Subjects			
Cushing's disease	80		
Ectopic ACTH secretion	1		
Adrenal dependent	8		
Unknown	5		
Body weight Units: kg			
arithmetic mean			
standard deviation	±	±	
Body mass index Units: kg/m2			
arithmetic mean			
standard deviation	±	±	
Time since diagnosis Units: months			
arithmetic mean			
standard deviation	±	±	
Baseline mUFC molar concentration Units: nmol/24 h			
arithmetic mean			

standard deviation	±	±	
Baseline mUFC mass concentration Units: ug/24 h arithmetic mean standard deviation	±	±	
Baseline mUFC x ULN Units: Multiples of ULN arithmetic mean standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Levoketoconazole Titration Phase

Reporting group description:

The initial dose was levoketoconazole 150 mg BID (300 mg/day), taken as 1 tablet in the morning and 1 tablet in the evening. During the first 2 to 21 weeks, dose was titrated in protocol-defined increments up to each subject's therapeutic dose, based on the subject's urinary free cortisol (UFC) levels and safety/tolerability. The interval between upward dose adjustments was to be approximately 18 days. The lowest allowed dose was 150 mg/day for subjects who could not tolerate 150 mg BID; the highest allowed dose was 600 mg BID (1200 mg/day).
The therapeutic dose had been reached when mean UFC levels (determined from a total of 4 24-h urine collections) were ≤ULN of the assay, or the maximum allowed dose (600 mg BID) had been reached, or a clinically meaningful partial response and the maximal tolerated dose had been reached.

Reporting group title	Levoketoconazole Maintenance Phase

Reporting group description:

Dosing was to be continued for 6 months at the therapeutic dose established by dose titration in the Titration Phase. During the Maintenance Phase, levoketoconazole dose was not to be changed unless medically necessary.

Reporting group title	Levoketoconazole Extended Evaluation Phase

Reporting group description:

During the Extended Evaluation Phase, levoketoconazole dosing was to continue as in the Maintenance Phase. Dosing was to be continued for 6 months. The levoketoconazole dose was not to be changed unless medically necessary.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received at least 1 dose of levoketoconazole. This population is used for the evaluation of efficacy and all safety analyses.

Subject analysis set title	ITT2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Identical to ITT

Primary: mUFC Complete Response Rate

End point title	mUFC Complete Response Rate

End point description:

Clinical response to levoketoconazole was defined as mean 24-h urinary free cortisol concentration (mUFC) less than or equal to the ULN (upper limit of normal) of the reference range following 6 months of therapy in the Maintenance Phase without a dose increase during that phase. The proportion of responders at the end of maintenance phase visit for all dose groups combined was estimated using a generalised linear model with repeated measurements and with region (US vs non-US), concurrent CS median conditions (diabetes [Yes/NO], hypertension [Yes/No]), age (rounded median split based on the ITT population), sex, disease duration (years), prior CS medication (Yes/No), prior radiation therapy (Yes/No) as baseline covariates and visit as an independent factor. The LS mean estimate of the UFC response after 6 months of treatment in maintenance phase with 95% confidence interval was used to infer efficacy.

End point type	Primary

End point timeframe:

6-month Maintenance Phase

End point values	ITT	ITT2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	94[1]		
Units: Proportion of responders				
least squares mean (standard error)	0.30 (± .05)	.30 (± .05)		

Notes:

[1] - Identical to ITT

Statistical analyses

Statistical analysis title	Primary Efficacy Endpoint Analysis

Statistical analysis description:

The GLM described above was used as the primary analysis method. Under the null hypothesis of at most 20% responders, 90 subjects in the ITT population provided 90% power with 2-sided type 1 error of 0.05 assuming an observed response of 35%. The Wald 95% confidence interval around the UFC response estimate provided by the GLM served as the primary basis of statistical inference.

Comparison groups	ITT v ITT2
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0154 [3]
Method	Generalized Linear Model
Parameter estimate	Proportion
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.4

Notes:

[2] - A superiority analysis comparing the observed ITT response to thg null hypothesized rate. Subjects were imputed as non-responders for the primary endpoint if they: withdrew prior to Month 6 of maintenance phase; had a dose increase relative to the therapeutic dose during maintenance phase; Month 6 mUFC data were missing or inadequate; had received radiation therapy and exhibited no rebound increase in mUFC following withdrawal of levoketoconazole immediately after the end of maintenance phase

[3] - The one-sided p-value calculated was based on a null hypothesis that true response is less than or equal 0.20.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reported TEAEs are summarized from the first day of study drug administration through the last day plus 30 days. For the ITT pop, median was ~14 (mean ~12, max ~23) months.

Adverse event reporting additional description:

Only treatment-emergent AEs are reported

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Levoketoconazole, all phases combined

Reporting group description:

All patients enroled and treated i.e. who receive at least one dose of study drug

Serious adverse events	Levoketoconazole, all phases combined		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 94 (17.02%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of the colon			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Benign ovarian tumour			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase			

increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hyphaema			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis chronic			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 94 (1.06%)		
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	Levoketoconazole, all phases combined		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 94 (97.87%)		
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 94 (19.15%)		
occurrences (all)	24		
General disorders and administration site conditions			
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 94 (19.15%)		
occurrences (all)	24		
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 94 (17.02%)		
occurrences (all)	20		
Asthenia			
alternative assessment type: Non-systematic			

subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	8		
Reproductive system and breast disorders			
Menstruation irregular			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	7		
Psychiatric disorders			
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 94 (8.51%)		
occurrences (all)	9		
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	7		
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 94 (15.96%)		
occurrences (all)	20		
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 94 (12.77%)		
occurrences (all)	13		
Gamma-glutamyltransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 94 (11.70%)		
occurrences (all)	16		

Electrocardiogram QT prolonged			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 94 (9.57%)		
occurrences (all)	13		
Blood alkaline phosphatase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Cardiac disorders			
Palpitations			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 94 (28.72%)		
occurrences (all)	52		
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 94 (12.77%)		
occurrences (all)	12		
Dysgeusia			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	7		
Gastrointestinal disorders			
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	31 / 94 (32.98%)		
occurrences (all)	44		
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 94 (14.89%)		
occurrences (all)	17		
Vomiting			

alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 94 (10.64%)		
occurrences (all)	16		
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 94 (9.57%)		
occurrences (all)	9		
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	9		
Gastrooesophageal reflux disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Dry skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 94 (11.70%)		
occurrences (all)	11		
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 94 (9.57%)		
occurrences (all)	9		
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 94 (8.51%)		
occurrences (all)	11		
Hyperhidrosis			
alternative assessment type: Non-systematic			

subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	7		
Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 94 (14.89%)		
occurrences (all)	14		
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 94 (9.57%)		
occurrences (all)	12		
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	7		
Musculoskeletal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	6		
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	6		
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 94 (12.77%)		
occurrences (all)	18		
Urinary tract infection			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	11 / 94 (11.70%) 11		
Metabolism and nutrition disorders Hypokalaemia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Decreased appetite alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 13 / 94 (13.83%) 14 5 / 94 (5.32%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2014	- Increase in window for time between dose adjustments from ±2 to ±7 days - Increase in duration of screening phase from 8 to about 12 weeks - Allowance of screening assessments to occur following ICF signature and discontinuation of prohibited medications
16 April 2015	- Removal of ambulatory blood pressure assessments; physician and subject VAS questionnaires; option for TID dosing - Addition of the CushingQOL and BDI-II - Modification of LNSC to be measured over 2 instead of 3 nights - Decrease in number of PK samples to be collected
25 October 2016	- Removal of: FU visit for patients participating in Expanded Access Program; extra 24-h urine collection at start of Maintenance Phase; magnetic resonance imaging at FU visit for patients completing Month 12 of the Extended Evaluation phase - Addition of: guidance for rescreening; PK sampling with persistent and confirmed QTc prolongation; visit windows (±7 and ±14 days) during Maintenance and Extended Evaluation phases, respectively; hypothesis testing for clinical laboratory values, vital signs and ECG - Increase in washout period for pasireotide LAR from 8 to 12 weeks - Clarification added regarding expected values for normal 24-h creatinine excretion rates - Clarifications added on prohibited and precautionary medications use - Clarification added regarding data restriction plan (for availability of efficacy data during conduct of the study) - Realigned secondary and exploratory objectives and endpoints - Clarified analytical methods for some secondary and exploratory endpoints

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.

None

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33216275

http://www.ncbi.nlm.nih.gov/pubmed/31542384