Clinical trial results:
A Phase III, multi-center, double-blind, randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease (CD)

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.nov for complete trial results.

Summary

EudraCT number	2013-004766-34
Trial protocol	IT GB DE AT ES NL FR
Global end of trial date	04 December 2019
Results information	
Result version number	v1 (current)
This version publication date	31 October 2020
First version publication date	31 October 2020

Trial information

Trial identification	
Sponsor protocol code	CLCI699C2301
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02180217
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 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the complete response rate at the end of the 8-week period of randomized withdrawal (Week 34) between patients randomized to continued osilodrostat therapy vs. placebo.

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 October 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	Argentina: 2
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	China: 4
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	India: 7
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Netherlands: 4

Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	137
EEA total number of subjects	50

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)	130
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

132 patients were planned, 137 were enrolled and 137 were analyzed.

Pre-assignment

Screening details:

132 patients were planned, 137 were enrolled and 137 were analyzed.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	osilodrostat (LCI699)

Arm description:

Consisted of a single-arm, open-label, osilodrostat dose-titration in individual patients and then osilodrostat during a double-blind, placebo controlled RW Period.

Arm type	Experimental
Investigational medicinal product name	osilodrostat
Investigational medicinal product code	LCI699
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Osilodrostat was supplied in strengths of 1 mg, 5 mg, 10 mg, and 20 mg. The maximum dose of osilodrostat was 30 mg bid. Osilodrostat dosing regimen included up-titration following a 2 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, and 30 mg bid escalation sequence. If hypocortisolism occurred at 2 mg bid, the dose was lowered to 1 mg bid. The up-titration continued until the mUFC ≤ upper normal of limit (ULN).

Arm title	LCI699 Placebo

Arm description:

Consisted of a single-arm, open-label, osilodrostat dose-titration in individual patients and then placebo during a double-blind, placebo controlled RW Period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	LCI699 placebo
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets had the same size, color and imprint as the 1 mg, 5 mg, 10 mg, and 20 mg osilodrostat tablets.

Arm title	Non-randomized

Arm description:

All participants in this group took open label osilodrostat, before and after randomization.

Arm type	Experimental

Investigational medicinal product name	Osilodrostat
Investigational medicinal product code	LCI699
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Osilodrostat was supplied in strengths of 1 mg, 5 mg, 10 mg, and 20 mg. The maximum dose of osilodrostat was 30 mg bid. Osilodrostat dosing regimen included up-titration following a 2 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, and 30 mg bid escalation sequence. If hypocortisolism occurred at 2 mg bid, the dose was lowered to 1 mg bid. The up-titration continued until the mUFC ≤ upper normal of limit (ULN).

Number of subjects in period 1	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized
Started	36	35	66
Discontinued at/prior to Week 12 (W12)	0 [1]	0 [2]	7 [3]
Discont. at/prior to W26 but after W12	0 [4]	0 [5]	12 [6]
Discontinued prior to W48 but after W26	0 [7]	2 [8]	3 [9]
Completed Week 48 (Core Phase)	36	33	44
Completed W48, did not enter Ext. phase	1 [10]	3 [11]	3 [12]
Completed W48, entered Ext. phase	35	30	41
Discontinued Extension Phase	12 [13]	6 [14]	16 [15]
Completed Ext. Phase	23 [16]	24 [17]	25 [18]
Completed	24	27	28
Not completed	12	8	38
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	1	1	4
Physician decision	1	1	6
Adverse event, non-fatal	3	2	22
Unsatisfactory therapeutic effect	1	-	-
Subject/Guardian decision	5	3	6

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[13] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[14] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[15] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[16] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm
[17] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.

Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm

[18] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects dropped off at different time points, thus changing the number of subjects in the arm

Baseline characteristics

Reporting groups	
Reporting group title	osilodrostat (LCI699)
Reporting group description:	
Consisted of a single-arm, open-label, osilodrostat dose-titration in individual patients and then osilodrostat during a double-blind, placebo controlled RW Period.	
Reporting group title	LCI699 Placebo
Reporting group description:	
Consisted of a single-arm, open-label, osilodrostat dose-titration in individual patients and then placebo during a double-blind, placebo controlled RW Period.	
Reporting group title	Non-randomized
Reporting group description:	
All participants in this group took open label osilodrostat, before and after randomization.	

Reporting group values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized
Number of subjects	36	35	66
Age categorical Units: Subjects			
Adults (18-64 years)	34	34	62
From 65-84 years	2	1	4
Age Continuous Units: years			
arithmetic mean	44.3	42.0	39.0
standard deviation	± 11.27	± 13.47	± 13.38
Sex: Female, Male Units: Participants			
Female	30	22	54
Male	6	13	12
Race/Ethnicity, Customized Units: Subjects			
Caucasian	27	23	39
Black	0	3	1
Asian	7	7	25
Other	2	2	1

Reporting group values	Total		
Number of subjects	137		
Age categorical Units: Subjects			
Adults (18-64 years)	130		
From 65-84 years	7		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	106		

Male	31		

Race/Ethnicity, Customized Units: Subjects			
Caucasian	89		
Black	4		
Asian	39		
Other	5		

End points

End points reporting groups

Reporting group title	osilodrostat (LCI699)
Reporting group description:	
Consisted of a single-arm, open-label, osilodrostat dose-titration in individual patients and then osilodrostat during a double-blind, placebo controlled RW Period.	
Reporting group title	LCI699 Placebo
Reporting group description:	
Consisted of a single-arm, open-label, osilodrostat dose-titration in individual patients and then placebo during a double-blind, placebo controlled RW Period.	
Reporting group title	Non-randomized
Reporting group description:	
All participants in this group took open label osilodrostat, before and after randomization.	
Subject analysis set title	All Participants
Subject analysis set type	Full analysis
Subject analysis set description:	
Consisted of all participants who were enrolled and treated with open label osilodrostat.	
Subject analysis set title	All participants (Escape analysis)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Consisted of all participants in the study under osilodrostat treatment. This is a subset of the Full analysis set which excludes patients randomized to placebo and patients that did not have mUFC <=ULN at any stage on the trial	
Subject analysis set title	osilodrostat (LCI699) 2 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received 2mg of osilodrostat	
Subject analysis set title	osilodrostat (LCI699) 3 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received 3mg of osilodrostat	
Subject analysis set title	osilodrostat (LCI699) 5 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received 5 mg of osilodrostat	
Subject analysis set title	osilodrostat (LCI699) 7 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received 7 mg of osilodrostat	

Primary: Percentage of primary efficacy responder at Week 34 by randomized treatment and strata

End point title	Percentage of primary efficacy responder at Week 34 by randomized treatment and strata[1]
End point description:	
To compare the complete response rate at the end of the 8-week period of randomized withdrawal between randomized patients.A primary efficacy responder is defined as a randomized patient who has mUFC ≤ ULN at Week 34 and who was neither discontinued (study or RW treatment) nor had osilodrostat dose increase above the level at Week 26 during the RW Period of the study. mUFC: mean urinary free cortisol; ULN: Upper Limit of Normal	
End point type	Primary

End point timeframe:

Week 34 (8 weeks)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not planned for this endpoint.

End point values	osilodrostat (LCI699)	LCI699 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: Percentage of participants				
number (not applicable)	86.1	29.4		

Statistical analyses

Statistical analysis title	CMH exact test: Osilodrostat vs. Placebo
Comparison groups	osilodrostat (LCI699) v LCI699 Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	13.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.73
upper limit	53.44

Secondary: Percentage of secondary efficacy responder at Week 24 (Key Secondary endpoint)

End point title	Percentage of secondary efficacy responder at Week 24 (Key Secondary endpoint)

End point description:

To assess the complete response rate at the end of individual dose-titration and treatment with LCI699 in the initial single-arm, open label period. A Key secondary efficacy responder is defined as a patient in FAS who has mUFC ≤ ULN at Week 24 and the dose of osilodrostat during Study Period 2 (Weeks 13-24) was not increased above the level established at the end of Study Period 1 (Week 12). Patients who had missing mUFC assessment at Week 24 will be counted as non-responders for the key secondary endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	All Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	137			
Units: Percentage of participants				
number (confidence interval 95%)	52.6 (43.9 to 61.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-loss of control of mean urinary free cortisol (mUFC) by randomized treatment group

End point title	Time-to-loss of control of mean urinary free cortisol (mUFC) by randomized treatment group[2]

End point description:

Time-to-loss of control of mUFC during the RW Period, defined as the time (in days) from randomization to the first evidence of loss of control (defined as mUFC assessment >1.5 ULN based on central laboratory result & at least 2 of the associated individual urine samples showing UFC >1.5×ULN) within the RW period. A patient without evidence of loss of control was censored at the date of the last assessment with mUFC ≤ 1.5 ULN. If a patient discontinued randomized treatment without having a UFC assessment, they were censored at the date of randomization. The measure type (number) refers to an Event probability estimate 8 weeks after randomization.

End point type	Secondary

End point timeframe:

8 weeks after randomization

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not planned for this endpoint.

End point values	osilodrostat (LCI699)	LCI699 Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: Percentage				
number (confidence interval 95%)	5.6 (1.4 to 20.4)	61.1 (45.0 to 77.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate (CRR)

End point title	Complete Response Rate (CRR)

End point description:

Complete response rate is defined as percentage of enrolled participants with mUFC ≤ ULN

End point type	Secondary

End point timeframe:

Week 12, Week 24, Week 48, Week 72, last observed value

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: Percentage of participants				
number (not applicable)				
Week 12	86.1	91.4	53.0	
Week 24	100.0	97.1	34.8	
Week 48	88.9	77.1	48.5	
Week 72	82.9	83.3	78.0	
Last observed value	69.4	74.3	53.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mUFC (actual and percentage change)

End point title	Change from baseline in mUFC (actual and percentage change)
End point description:	
Actual and percentage change in mUFC from baseline.	
End point type	Secondary
End point timeframe:	
Weeks 12, 24, 48, 72, last available assessment	

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: nmol/24h				
arithmetic mean (standard deviation)				
Actual Baseline (BL)	890.0 (± 1275.66)	560.0 (± 548.84)	1305.8 (± 2012.21)	
Wk 12: % change from BL (n = 33,34,58)	-80.6 (± 19.28)	-81.7 (± 15.08)	-74.9 (± 26.66)	
Wk 24: % change from BL (n=36,35,54)	-77.4 (± 34.04)	-79.6 (± 18.35)	-62.5 (± 61.56)	
Wk 48: % change from BL (n = 34,32,42)	-84.9 (± 13.70)	-80.5 (± 18.68)	-76.4 (± 34.39)	
Wk 72: % change from BL (n= 32,29,35)	-78.6 (± 33.09)	-79.5 (± 18.99)	-72.3 (± 50.93)	
Last avail. assess. % change from BL	-71.0 (± 48.20)	-57.3 (± 66.80)	-47.3 (± 80.78)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Fasting glucose

End point title	Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Fasting glucose

End point description:

Percentage change in fasting glucose from baseline.

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 72, last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n = 34, 33, 62)	102.7 (± 35.23)	90.5 (± 18.53)	101.8 (± 31.00)	
Wk 48: (n = 33,30,38)	-3.1 (± 21.18)	-4.7 (± 11.11)	-12.4 (± 14.55)	
Wk 72: (n = 30,25,32)	0.9 (± 15.91)	-3.5 (± 13.57)	-8.8 (± 15.72)	
Last avail. assessment (n = 34,32,62)	-2.4 (± 29.32)	-0.2 (± 18.09)	-11.6 (± 16.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Hemoglobin A1C (HbA1C)

End point title	Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Hemoglobin A1C (HbA1C)

End point description:

Percentage change in glycosylated hemoglobin (HbA1c) from baseline.

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 72, last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: percentage				
arithmetic mean (standard deviation)				
Baseline	6.1 (± 0.98)	5.8 (± 0.93)	6.0 (± 0.97)	
Wk 48: (n = 35, 33, 42)	-4.2 (± 11.48)	-6.0 (± 8.31)	-5.8 (± 8.86)	
Wk 72: (n = 33,29,35)	-5.7 (± 8.88)	-6.1 (± 6.61)	-6.5 (± 8.88)	
Last avail. assessment	-4.9 (± 10.66)	-2.8 (± 7.49)	-4.5 (± 9.46)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Cholesterol, LDL Cholesterol, HDL Cholesterol & Triglyceride

End point title	Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Cholesterol, LDL Cholesterol, HDL Cholesterol & Triglyceride

End point description:

Percentage change in Cholesterol, LDL Cholesterol, HDL Cholesterol & Triglyceride from baseline.

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 72, last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: mmol/L				
arithmetic mean (standard deviation)				
Cholesterol: BL (n = 36, 34, 66)	5.5 (± 1.22)	5.3 (± 0.90)	5.1 (± 1.24)	
Cholesterol: Wk 48: (n = 35,32,41)	-11.6 (± 15.71)	-6.3 (± 13.64)	-8.5 (± 17.59)	
Cholesterol: Wk 72: (n = 33,27,33)	-6.3 (± 16.62)	-6.6 (± 14.73)	-5.4 (± 19.47)	
Cholesterol: Last avail. assessment	-3.6 (± 20.83)	-5.4 (± 16.25)	-4.6 (± 22.09)	
LDL Cholesterol: BL	3.2 (± 1.09)	3.1 (± 0.77)	2.9 (± 0.94)	
LDL Cholesterol: Wk 48 (n=35,32,40)	-9.5 (± 23.43)	-5.1 (± 20.31)	-2.1 (± 31.96)	
LDL Cholesterol: Wk 72 (n=33,27,33)	-5.0 (± 25.03)	-5.4 (± 24.86)	2.3 (± 33.70)	
LDL Cholesterol: Last avail asses. (n=36,34,65)	0.0 (± 33.36)	-3.8 (± 23.37)	2.0 (± 42.86)	
HDL Cholesterol: BL (n=36,34,66)	1.7 (± 0.55)	1.5 (± 0.36)	1.6 (± 0.42)	
HDL Cholesterol: Wk 48 (n=35,32,41)	-14.7 (± 16.47)	-9.8 (± 9.79)	-17.9 (± 18.17)	
HDL Cholesterol: Wk 72 (n=33,27,33)	-9.7 (± 20.20)	-9.7 (± 16.38)	-16.5 (± 15.87)	
HDL Cholesterol: Last avail assess. (n=36,34,66)	-8.5 (± 19.62)	-6.3 (± 17.40)	-13.4 (± 21.98)	

Triglyceride: BL (n= 36,34,66)	1.5 (± 0.78)	1.4 (± 0.62)	1.6 (± 1.74)	
Triglyceride: Wk 48 (n= 35,32,41)	-3.7 (± 28.68)	0.8 (± 36.56)	16.8 (± 160.90)	
Triglyceride: Wk 72 (n=33,28,33)	1.9 (± 37.12)	0.2 (± 42.41)	0.8 (± 36.50)	
Triglyceride: Last avail. Assess. (n= 36,34, 66)	3.1 (± 35.61)	-0.3 (± 42.60)	20.4 (± 92.91)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Sitting systolic blood pressure (SBP) & sitting diastolic blood pressure (DBP)

End point title	Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Sitting systolic blood pressure (SBP) & sitting diastolic blood pressure (DBP)

End point description:

Percentage change in sitting SBP & DBP from baseline.

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 72, last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: mmHg				
arithmetic mean (standard deviation)				
SBP: Baseline	132.2 (± 15.44)	128.8 (± 11.93)	134.0 (± 16.34)	
SBP: Wk 48: (n = 35,33,43)	-10.7 (± 12.44)	-3.4 (± 9.52)	-6.2 (± 11.14)	
SBP: Wk 72: (n = 34,29,36)	-8.4 (± 11.81)	-5.6 (± 15.60)	-5.9 (± 13.89)	
SBP: Last avail. assessment	-5.3 (± 10.96)	-3.1 (± 11.53)	-7.4 (± 11.00)	
DBP: Baseline	85.3 (± 11.38)	85.0 (± 10.03)	85.4 (± 10.53)	
DBP: Wk 48: (n = 35,33,43)	-8.1 (± 13.22)	-5.4 (± 11.29)	-6.3 (± 13.50)	
DBP: Wk 72: (n = 34,29,36)	-5.6 (± 13.05)	-7.7 (± 11.76)	-4.5 (± 15.15)	
DBP: Last avail. assessment	-2.7 (± 13.92)	-3.4 (± 12.88)	-5.3 (± 12.13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Weight

End point title	Percentage change from baseline in cardiovascular-related

	parameter associated with Cushing's disease: Weight
End point description:	
Percentage change in weight from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 48, 72, last available assessment	

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: kg				
arithmetic mean (standard deviation)				
Baseline	78.2 (± 19.02)	83.4 (± 24.73)	80.7 (± 23.06)	
Wk 48: (n = 36,33,43)	-3.9 (± 6.56)	-4.8 (± 6.45)	-5.0 (± 7.17)	
Wk 72: (n = 34,29,36)	-4.3 (± 7.67)	-6.2 (± 6.99)	-6.8 (± 8.58)	
Last avail. assessment	-3.4 (± 9.69)	-4.6 (± 9.86)	-4.9 (± 7.78)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Body Mass Index (BMI)

End point title	Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Body Mass Index (BMI)
End point description:	
Percentage change in BMI from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 48, 72, last available assessment	

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: kg/m^2				
arithmetic mean (standard deviation)				
Baseline	29.6 (± 7.36)	30.9 (± 8.38)	30.4 (± 7.74)	
Wk 48: (n = 36,33,43)	-3.9 (± 6.56)	-4.7 (± 6.46)	-5.0 (± 7.18)	
Wk 72: (n = 34,29,36)	-4.3 (± 7.68)	-6.2 (± 6.92)	-6.8 (± 8.63)	
Last avail. assessment	-3.3 (± 9.68)	-4.7 (± 9.85)	-4.9 (± 7.80)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Waist Circumference

End point title	Percentage change from baseline in cardiovascular-related parameter associated with Cushing's disease: Waist Circumference

End point description:

Percentage change in waist circumference from baseline.

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 72, last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: cm				
arithmetic mean (standard deviation)				
Baseline	100.5 (± 16.81)	103.7 (± 18.26)	105.0 (± 21.15)	
Wk 48: (n = 34,32,43)	-4.8 (± 5.90)	-3.5 (± 10.53)	-4.3 (± 6.43)	
Wk 72: (n = 33,29,36)	-5.1 (± 7.18)	-5.5 (± 10.23)	-7.0 (± 7.25)	
Last avail. assessment (n =35,33,65)	-4.9 (± 6.44)	-4.6 (± 11.61)	-5.3 (± 8.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in Patient-Reported Outcomes (Cushing's Health-Related Quality of Life (QoL)) - Total score

End point title	Percentage change from baseline in Patient-Reported Outcomes (Cushing's Health-Related Quality of Life (QoL)) - Total score

End point description:

Change in standardized score of Cushing QoL from baseline to Week 24 and Week 48. The Cushing’s Disease Health-Related Quality of Life Questionnaire (CushingQoL) (version 1.0) was developed to evaluate quality of life in patients with Cushing’s syndrome. The CushingQoL is comprised of 12 items that capture patient responses on seven concepts: daily activities, healing and pain, mood and self-confidence, social concerns, physical appearance, memory and concern about the future. Content reliability, sensitivity to change and psychometric properties have been validated in patients with Cushing’s disease. Patients were asked to complete the questionnaire prior to clinical assessments being

undertaken. Increase from baseline for Cushing QoL total score are indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline, Week (W) 48, W72, Last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: scales on a score				
arithmetic mean (standard deviation)				
Baseline (Actual)	44.4 (± 18.33)	43.2 (± 22.45)	40.5 (± 17.61)	
Week 48 (n = 35,32,43)	60.2 (± 128.33)	40.3 (± 70.71)	54.9 (± 112.79)	
Week 72 (n = 32,28, 37)	64.4 (± 158.86)	57.6 (± 92.37)	60.9 (± 125.13)	
Last available assess. (n = 36,35,65)	68.7 (± 172.98)	58.3 (± 125.29)	52.9 (± 109.56)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in Patient-Reported Outcomes: Beck Depression Inventory-II (BDI-II)

End point title	Percentage change from baseline in Patient-Reported Outcomes: Beck Depression Inventory-II (BDI-II)

End point description:

Change in standardized score of Beck Depression Inventory-II (BDI-II0 from baseline to Week 24 and Week 48. The Beck Depression Inventory II (BDI-II) is a patient reported instrument that consists of 21 items designed to assess the intensity of depression in clinical and normal patients in the preceding two weeks. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression. Patients were asked to complete the questionnaire prior to clinical assessments being undertaken. A reduction from baseline in BDI-II is indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline, W48, W72, Last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: scores on a a scale				
arithmetic mean (standard deviation)				
Baseline	15.1 (± 11.14)	17.8 (± 9.93)	17.3 (± 10.67)	
W48 (n = 33,31,43)	-17.2 (± 97.71)	-38.7 (± 42.90)	-35.6 (± 60.50)	

W72 (n = 30,27,36)	4.7 (± 230.64)	-39.0 (± 48.62)	-44.3 (± 62.46)	
Last avail. assess.(n = 34,34,64)	-15.7 (± 125.96)	-41.8 (± 46.25)	-13.8 (± 86.05)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in Patient-Reported Outcomes: EQ-5D-5L utility index

End point title	Percentage change in Patient-Reported Outcomes: EQ-5D-5L utility index

End point description:

Change in standardized score of EQ-5D-5L utility index from baseline to Week 24 and Week 48. The EQ-5D-5L questionnaire is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The EQ-5D-5L is designed for self-completion by respondents and is cognitively undemanding, taking only a few minutes to complete. The EQ-5D-5L measures 5 items on mobility, self-care, usual activities, pain/discomfort, anxiety/depression, measured on 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. A single index value is analyzed for the EQ-5D-5L score. An increase from baseline in EQ-5D-5L is indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline, W48, W72, Last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline	0.7 (± 0.24)	0.7 (± 0.24)	0.7 (± 0.28)	
Week 48 (n = 35,32,43)	19.9 (± 46.91)	-12.5 (± 80.08)	142.0 (± 854.94)	
Week 72 (n= 32,28,36)	24.2 (± 49.58)	-8.6 (± 88.16)	137.1 (± 706.16)	
Last avail. assess. (n = 36,35,65)	19.5 (± 49.47)	-12.4 (± 91.85)	64.0 (± 534.01)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in Patient-Reported Outcomes: EQ-5D-5L vascular analog scale (VAS)

End point title	Percentage change in Patient-Reported Outcomes: EQ-5D-5L

	vascular analog scale (VAS)

End point description:

Change in standardized score of EQ-5D-5L VAS from baseline to Week 24 and Week 48. The EQ-5D-5L also includes a 20 cm vertical, VAS (visual analogue scale) with on a scale of 0-100, with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. A single index value is analyzed for the VAS score. An increase from baseline in EQ-5D-5L VAS is indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline, W48, W72, Last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline	61.3 (± 18.97)	64.2 (± 16.37)	60.8 (± 21.09)	
Week 48 (n = 35,31,43)	29.7 (± 62.35)	13.9 (± 22.93)	30.5 (± 82.96)	
Week 72 (n= 32,27,36)	28.6 (± 56.36)	13.8 (± 26.38)	34.6 (± 94.43)	
Last avail. assess. (n = 36,35,65)	29.9 (± 56.00)	14.4 (± 32.27)	23.5 (± 82.72)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the physical features of Cushing's disease by photography

End point title	Change from baseline in the physical features of Cushing's disease by photography

End point description:

Improvement from baseline to Weeks 48, 72 and End of Treatment (Extension period) in each of the following clinical signs of Cushing's disease by photography: facial rubor, hirsutism, striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises).

End point type	Secondary

End point timeframe:

Week 48, Week 72, Last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: Percentage of participants				
number (confidence interval 95%)				
W48: Facial rubor (n=30,30,37)	50.0 (31.3 to 68.7)	46.7 (28.3 to 65.7)	43.2 (27.1 to 60.5)	

W48: Striae (n=30,30, 37)	30.0 (14.7 to 49.4)	23.3 (9.9 to 42.3)	40.5 (24.8 to 57.9)	
W48:Supraclavicular fat pad(n=30,30, 37)	56.7 (37.4 to 74.5)	43.3 (25.5 to 62.6)	54.1 (36.9 to 70.5)	
W48: Dorsal fat pad(n=30,30, 37)	60.0 (40.6 to 77.3)	40.0 (22.7 to 59.4)	56.8 (39.5 to 72.9)	
W48: Proximal muscle atrophy(n=30,30, 37)	40.0 (22.7 to 59.4)	26.7 (12.3 to 45.9)	45.9 (29.5 to 63.1)	
W48: Central obesity(n=30,30, 37)	43.3 (25.5 to 62.6)	30.0 (14.7 to 49.4)	51.4 (34.4 to 68.1)	
W48: Ecchymoses (n=30,30, 37)	33.3 (17.3 to 52.8)	26.7 (12.3 to 45.9)	43.2 (27.1 to 60.5)	
W72: Facial rubor (n=29,27, 30)	48.3 (29.4 to 67.5)	55.6 (35.3 to 74.5)	53.3 (34.3 to 71.7)	
W72: Striae (n=29,27, 30)	27.6 (12.7 to 47.2)	25.9 (11.1 to 46.3)	36.7 (19.9 to 56.1)	
W72:Supraclavicular fat pad(n=29,27, 30)	55.2 (35.7 to 73.6)	51.9 (31.9 to 71.3)	53.3 (34.3 to 71.1)	
W72: Dorsal fat pad(n=29,27, 30)	69.0 (49.2 to 84.7)	48.1 (28.7 to 68.1)	53.3 (34.3 to 71.7)	
W72: Proximal muscle atrophy(n=29,27, 30)	31.0 (15.3 to 50.8)	25.9 (11.1 to 46.3)	46.7 (28.3 to 65.7)	
W72: Central obesity(n=29,27, 30)	37.9 (20.7 to 57.7)	37.0 (19.4 to 57.6)	43.3 (25.5 to 62.6)	
W72: Ecchymoses (n=29,27,30)	27.6 (12.7 to 47.2)	29.6 (13.8 to 50.2)	36.7 (19.9 to 56.1)	
End of Trial (EOT):Facial rubor (n=25,23,26)	60.0 (38.7 to 78.9)	56.5 (34.5 to 76.8)	53.8 (33.4 to 73.4)	
EOT: Striae (n=25,23,26)	32.0 (14.9 to 53.5)	34.8 (16.4 to 57.3)	30.8 (14.3 to 51.8)	
EOT:Supraclavicular fat pad(n=25,23,26)	52.0 (31.3 to 72.2)	43.5 (23.2 to 65.5)	42.3 (23.4 to 63.1)	
EOT: Dorsal fat pad (n=25,23, 26)	56.0 (34.9 to 75.6)	52.2 (30.6 to 73.2)	46.2 (26.6 to 66.6)	
EOT: Proximal muscle atrophy (n=25,23,26)	36.0 (18.0 to 57.5)	21.7 (7.5 to 43.7)	50.0 (29.9 to 70.1)	
EOT: Central obesity (n=25,23,26)	40.0 (21.1 to 61.3)	39.1 (19.7 to 61.5)	38.5 (20.0 to 59.4)	
EOT: Ecchymoses (n=25,23, 26)	28.0 (12.1 to 49.4)	39.1 (19.7 to 61.5)	38.5 (20.2 to 59.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bone mineral density - All participants

End point title	Change from baseline in bone mineral density - All participants

End point description:

Actual and percent change from baseline to Week 48 and the LOV in bone mineral density as measured by DXA scan at the lumbar spine and total hip. An increase in bone mineral density is indicative of an improvement..

End point type	Secondary

End point timeframe:

Baseline, Week 48, Last observed value (LOV)

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: g/cm2				
arithmetic mean (standard error)				
Baseline (L1-L4 Lumbar Spine): actual	1.0 (± 0.20)	1.0 (± 0.17)	1.0 (± 0.18)	
W48 (L1-L4 Lumbar Spine): actual (n=23,23,35)	1.0 (± 0.19)	1.0 (± 0.17)	1.0 (± 0.19)	
W48 (L1-L4 Lumbar Spine): % change (n=23,23,35)	1.3 (± 5.33)	2.7 (± 5.06)	4.3 (± 7.69)	
LOV (L1-L4 Lumbar Spine): actual (n=26,24,46)	1.0 (± 0.20)	1.0 (± 0.18)	1.0 (± 0.18)	
LOV (L1-L4 Lumbar Spine): % change (n=26,24,46)	3.2 (± 6.31)	4.6 (± 7.55)	5.2 (± 6.37)	
Baseline (Total Hip): actual	0.9 (± 0.18)	0.8 (± 0.15)	0.9 (± 0.16)	
W48 (Total Hip): actual (n = 24,21,35)	0.9 (± 0.17)	0.8 (± 0.14)	0.9 (± 0.16)	
W48 (Total Hip): % change (n = 24,21,35)	-0.2 (± 8.00)	0.3 (± 4.91)	0.8 (± 3.43)	
LOV (Total Hip): actual (n = 27,22, 46)	0.9 (± 0.17)	0.8 (± 0.13)	0.9 (± 0.16)	
LOV (Total Hip): % change (n = 27,22, 46)	0 (± 8.54)	2.1 (± 6.31)	1.8 (± 3.70)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-escape

End point title	Time-to-escape

End point description:

Escape was defined as the time (in days) from the first mUFC ≤ ULN to the first mUFC results > 1.5 x ULN with at least 2 individual UFC results > 1.5 x ULN the loss happened beyond 12-week dose titration period. Participants randomized to placebo were not included in the analysis.

End point type	Secondary

End point timeframe:

From the first mUFC ≤ ULN to the first mUFC results > 1.5 x ULN with at least 2 individual UFC results > 1.5 x ULN

End point values	All participants (Escape analysis)			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: days				
median (confidence interval 95%)	546.0 (212.0 to 968.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: LCI699 exposures

End point title	LCI699 exposures

End point description:

To evaluate exposures of LCI699 in patients with Cushing's disease. Plasma concentrations (predose, 0.75 h, 1.5 h, and 4 h post-dose) of LCI699. These are the maximum number of PAS subjects analyzed for each incident dose. All 999 data represent not applicable (NA) values.

End point type	Secondary

End point timeframe:

from week 2 to 10 at Predose, 0.75h, 1.5h, and 4h post-dose

End point values	osilodrostat (LCI699) 2 mg	osilodrostat (LCI699) 3 mg	osilodrostat (LCI699) 5 mg	osilodrostat (LCI699) 7 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	132	39	105	24
Units: unit				
geometric mean (geometric coefficient of variation)				
Week (Wk) 2: Predose (n = 79,0,0,0)	1.904 (± 110.4)	999 (± 999)	999 (± 999)	999 (± 999)
Wk 2: 0.75h (n = 14,0,0,0)	1.907 (± 132.5)	999 (± 999)	999 (± 999)	999 (± 999)
Wk 2: 1.5h (n = 3,0,0,0)	5.1 (± 62.7)	999 (± 999)	999 (± 999)	999 (± 999)
Wk 2: 4h (n = 18,0,0,0)	5.818 (± 66.3)	999 (± 999)	999 (± 999)	999 (± 999)
Wk 4: Predose (n= 50,2,31,0)	2.104 (± 108.0)	2.898 (± 109.1)	3.584 (± 126.3)	999 (± 999)
Wk 4: 0.75h (n= 2,0,9,0)	0.859 (± 254.3)	999 (± 999)	7.091 (± 137.8)	999 (± 999)
Wk 4: 1.5h (n = 2,0,1,0)	8.737 (± 3.6)	999 (± 999)	24.2 (± 999)	999 (± 999)
Wk 4: 4h (n = 1,0,9,0)	8.930 (± 999)	999 (± 999)	15.985 (± 48.3)	999 (± 999)
Wk 6: Predose (n = 17,3,46,2)	2.037 (± 63.5)	2.392 (± 285.6)	5.087 (± 122.9)	8.065 (± 8.6)
Wk 6: 0.75h (n = 1,0,5,0)	3.110 (± 999)	999 (± 999)	5.223 (± 229.4)	999 (± 999)
Wk 6: 1.5h (n = 0,1,1,0)	999 (± 999)	22.4 (± 999)	21.4 (± 999)	999 (± 999)
Wk 6: 4h (n = 1,1,5,0)	8.380 (± 999)	18.6 (± 999)	18.373 (± 36.5)	999 (± 999)
Wk 8: Predose (n = 13,5,35,3)	2.198 (± 108.9)	4.061 (± 67.4)	4.487 (± 106.9)	6.718 (± 34.2)
Wk 8: 0.75h (n = 0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
Wk 8: 1.5h (n = 1,1,0,1)	10.8 (± 999)	20.4 (± 999)	999 (± 999)	32.1 (± 999)
Wk 8: 4h (n = 1,0,0,1)	6.65 (± 999)	999 (± 999)	999 (± 999)	32 (± 999)

Wk 10: Predose (n = 10,9,29,6)	1.862 (± 128.9)	3.007 (± 64.8)	4.704 (± 106.8)	5.451 (± 93.1)
Wk 10: 0.75h (n = 0,1,0,1)	999 (± 999)	6.7 (± 999)	999 (± 999)	17.1 (± 999)
Wk 10: 1.5h (n = 1,1,1,0)	12.1 (± 999)	18.3 (± 999)	34.2 (± 999)	999 (± 999)
Wk 10: 4h (n = 0,1,1,1)	999 (± 999)	15.8 (± 999)	27.2 (± 999)	35.5 (± 999)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Complete Response Rate (CRR)

End point title	Percentage of participants with Complete Response Rate (CRR)

End point description:

Complete response rate is defined as percentage of enrolled participants with mUFC ≤ ULN.

End point type	Secondary

End point timeframe:

Week 12, Week 24, Week 48, Week 72, last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: Percentage of participants				
number (not applicable)				
Week 12	6.1	91.4	53.0	
Week 24	100	97.1	34.8	
Week 48	88.9	77.1	48.5	
Week 72	82.9	83.3	78.0	
Last observed value	69.4	74.3	53.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Partial Response Rate (PRR)

End point title	Percentage of participants with Partial Response Rate (PRR)

End point description:

Partial response rate is defined as percentage of enrolled participants with ≥ 50% reduction from baseline in mUFC, but mUFC>ULN)

End point type	Secondary

End point timeframe:

Week 12, Week 24, Week 48, Week 72, last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: Percentage of participants				
number (not applicable)				
Week 12	2.8	5.7	24.2	
Week 24	0.0	0.0	30.3	
Week 48	5.6	11.4	10.6	
Week 72	8.6	13.3	2.4	
Last observed value	22.2	11.4	22.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Overall Response Rate (ORR)

End point title	Percentage of participants with Overall Response Rate (ORR)

End point description:

Overall response rate is defined as percentage of enrolled participants with mUFC ≤ ULN or at least 50% reduction from baseline.

End point type	Secondary

End point timeframe:

Week 12, Week 24, Week 48, Week 72, last available assessment

End point values	osilodrostat (LCI699)	LCI699 Placebo	Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	66	
Units: Percentage of participants				
number (not applicable)				
Week 12	88.9	97.1	77.3	
Week 24	100	97.1	65.2	
Week 48	94.4	88.6	59.1	
Week 72	91.4	96.7	80.5	
Last avail data	91.7	85.7	75.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until 30 days after the last dose administration, up to maximum duration of about 245.1 weeks.

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	22.1

Reporting groups

Reporting group title	Osilodrostat

Reporting group description:

Osilodrostat

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Non-randomized

Reporting group description:

Non-randomized

Reporting group title	All Patients

Reporting group description:

All Patients

Serious adverse events	Osilodrostat	Placebo	Non-randomized
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 36 (36.11%)	10 / 35 (28.57%)	32 / 66 (48.48%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pituitary tumour			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pituitary tumour			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	4 / 66 (6.06%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour benign			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour invasion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord polyp			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Completed suicide			

subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Depression			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural headache			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic intracranial hypertension			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIth nerve paralysis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	3 / 66 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune neutropenia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis glandularis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	6 / 66 (9.09%)
occurrences causally related to treatment / all	1 / 1	1 / 1	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	3 / 66 (4.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glucocorticoid deficiency			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary infarction			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	3 / 66 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Keratitis fungal			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 137 (40.15%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pituitary tumour			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour benign			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Tumour invasion			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Metrorrhagia			

subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Uterine polyp				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory disorder				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vocal cord polyp			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Completed suicide			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Depression			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications				
Head injury				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural headache				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiopulmonary failure				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Cranial nerve disorder				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Idiopathic intracranial hypertension				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				

subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VIth nerve paralysis			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune neutropenia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Diplopia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visual impairment			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Cholelithiasis			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis glandularis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences causally related to treatment / all	11 / 11		
deaths causally related to treatment / all	0 / 0		
Adrenocortical insufficiency acute			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Glucocorticoid deficiency			

subjects affected / exposed	2 / 137 (1.46%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Inappropriate antidiuretic hormone secretion				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pituitary infarction				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pituitary-dependent Cushing's syndrome				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Foot deformity				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Groin pain				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				

subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic sinusitis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	4 / 137 (2.92%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Influenza				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Keratitis fungal				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 137 (0.73%)			
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 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 137 (0.73%)		
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	Osilodrostat	Placebo	Non-randomized
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 36 (94.44%)	35 / 35 (100.00%)	65 / 66 (98.48%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	6 / 66 (9.09%)
occurrences (all)	2	1	6
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 36 (13.89%)	5 / 35 (14.29%)	14 / 66 (21.21%)
occurrences (all)	5	9	17
Hypotension			

subjects affected / exposed	7 / 36 (19.44%)	3 / 35 (8.57%)	3 / 66 (4.55%)
occurrences (all)	10	3	3
Varicose vein			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Application site rash			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
Asthenia			
subjects affected / exposed	11 / 36 (30.56%)	5 / 35 (14.29%)	11 / 66 (16.67%)
occurrences (all)	18	5	14
Chest discomfort			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	4 / 66 (6.06%)
occurrences (all)	1	0	4
Chills			
subjects affected / exposed	1 / 36 (2.78%)	3 / 35 (8.57%)	2 / 66 (3.03%)
occurrences (all)	1	3	2
Fatigue			
subjects affected / exposed	8 / 36 (22.22%)	13 / 35 (37.14%)	24 / 66 (36.36%)
occurrences (all)	9	19	39
Gait disturbance			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	1 / 66 (1.52%)
occurrences (all)	0	2	1
Malaise			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	7 / 66 (10.61%)
occurrences (all)	1	2	7
Oedema			
subjects affected / exposed	1 / 36 (2.78%)	3 / 35 (8.57%)	5 / 66 (7.58%)
occurrences (all)	2	5	6
Oedema peripheral			

subjects affected / exposed	8 / 36 (22.22%)	5 / 35 (14.29%)	9 / 66 (13.64%)
occurrences (all)	10	5	13
Pain			
subjects affected / exposed	2 / 36 (5.56%)	3 / 35 (8.57%)	1 / 66 (1.52%)
occurrences (all)	2	6	1
Pyrexia			
subjects affected / exposed	4 / 36 (11.11%)	3 / 35 (8.57%)	13 / 66 (19.70%)
occurrences (all)	4	4	18
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	2 / 66 (3.03%)
occurrences (all)	0	2	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 36 (13.89%)	4 / 35 (11.43%)	10 / 66 (15.15%)
occurrences (all)	6	5	10
Dyspnoea			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	4 / 66 (6.06%)
occurrences (all)	2	1	4
Nasal congestion			
subjects affected / exposed	3 / 36 (8.33%)	0 / 35 (0.00%)	3 / 66 (4.55%)
occurrences (all)	4	0	5
Oropharyngeal pain			
subjects affected / exposed	3 / 36 (8.33%)	4 / 35 (11.43%)	7 / 66 (10.61%)
occurrences (all)	3	4	7
Rhinitis allergic			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	4 / 66 (6.06%)
occurrences (all)	0	0	4
Rhinorrhoea			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	4 / 66 (6.06%)
occurrences (all)	2	2	4
Psychiatric disorders			

Anxiety			
subjects affected / exposed	3 / 36 (8.33%)	2 / 35 (5.71%)	7 / 66 (10.61%)
occurrences (all)	3	2	9
Depression			
subjects affected / exposed	3 / 36 (8.33%)	3 / 35 (8.57%)	7 / 66 (10.61%)
occurrences (all)	4	4	9
Insomnia			
subjects affected / exposed	4 / 36 (11.11%)	2 / 35 (5.71%)	7 / 66 (10.61%)
occurrences (all)	4	2	8
Irritability			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	4 / 66 (6.06%)
occurrences (all)	1	2	4
Panic attack			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
Sleep disorder			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	5 / 66 (7.58%)
occurrences (all)	2	0	5
Investigations			
11-deoxycortisol increased			
subjects affected / exposed	3 / 36 (8.33%)	1 / 35 (2.86%)	2 / 66 (3.03%)
occurrences (all)	3	1	2
Activated partial thromboplastin time prolonged			
subjects affected / exposed	3 / 36 (8.33%)	1 / 35 (2.86%)	1 / 66 (1.52%)
occurrences (all)	4	1	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	4 / 66 (6.06%)
occurrences (all)	0	0	6
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	4 / 66 (6.06%)
occurrences (all)	0	0	4
Blood cholesterol increased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences (all)	2	0	3
Blood corticotrophin increased			

subjects affected / exposed	8 / 36 (22.22%)	6 / 35 (17.14%)	14 / 66 (21.21%)
occurrences (all)	10	6	14
Blood testosterone increased			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	13 / 66 (19.70%)
occurrences (all)	3	1	14
Cortisol decreased			
subjects affected / exposed	3 / 36 (8.33%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences (all)	3	0	3
Cortisol free urine decreased			
subjects affected / exposed	8 / 36 (22.22%)	2 / 35 (5.71%)	1 / 66 (1.52%)
occurrences (all)	9	3	1
Cortisol free urine increased			
subjects affected / exposed	6 / 36 (16.67%)	1 / 35 (2.86%)	1 / 66 (1.52%)
occurrences (all)	6	1	1
Haemoglobin decreased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	4	0	0
Hormone level abnormal			
subjects affected / exposed	5 / 36 (13.89%)	1 / 35 (2.86%)	12 / 66 (18.18%)
occurrences (all)	9	2	15
Lipase increased			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	1 / 66 (1.52%)
occurrences (all)	1	3	1
Low density lipoprotein increased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences (all)	2	0	2
Renin increased			
subjects affected / exposed	3 / 36 (8.33%)	0 / 35 (0.00%)	3 / 66 (4.55%)
occurrences (all)	4	0	4
Weight decreased			
subjects affected / exposed	2 / 36 (5.56%)	2 / 35 (5.71%)	5 / 66 (7.58%)
occurrences (all)	3	2	5
Weight increased			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	2 / 66 (3.03%)
occurrences (all)	1	2	2
Injury, poisoning and procedural			

complications			
Contusion			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	4 / 66 (6.06%)
occurrences (all)	1	2	6
Ligament sprain			
subjects affected / exposed	3 / 36 (8.33%)	1 / 35 (2.86%)	1 / 66 (1.52%)
occurrences (all)	3	1	1
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	2 / 36 (5.56%)	3 / 35 (8.57%)	3 / 66 (4.55%)
occurrences (all)	2	3	3
Nervous system disorders			
Amnesia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Carpal tunnel syndrome			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences (all)	3	2	0
Dizziness			
subjects affected / exposed	5 / 36 (13.89%)	4 / 35 (11.43%)	17 / 66 (25.76%)
occurrences (all)	6	5	25
Headache			
subjects affected / exposed	11 / 36 (30.56%)	7 / 35 (20.00%)	32 / 66 (48.48%)
occurrences (all)	23	10	61
Hypoaesthesia			
subjects affected / exposed	1 / 36 (2.78%)	4 / 35 (11.43%)	4 / 66 (6.06%)
occurrences (all)	1	6	4
Memory impairment			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	2 / 66 (3.03%)
occurrences (all)	2	1	2
Migraine			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	4 / 66 (6.06%)
occurrences (all)	0	1	4
Paraesthesia			

subjects affected / exposed	1 / 36 (2.78%)	4 / 35 (11.43%)	0 / 66 (0.00%)
occurrences (all)	1	5	0
Somnolence			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	3 / 66 (4.55%)
occurrences (all)	2	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 36 (11.11%)	5 / 35 (14.29%)	6 / 66 (9.09%)
occurrences (all)	6	8	6
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences (all)	2	0	1
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	2 / 66 (3.03%)
occurrences (all)	2	0	2
Eye pruritus			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	0	2	0
Photophobia			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	0	3	0
Vision blurred			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	4 / 66 (6.06%)
occurrences (all)	0	0	5
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	3 / 66 (4.55%)
occurrences (all)	3	2	5
Abdominal pain			
subjects affected / exposed	5 / 36 (13.89%)	2 / 35 (5.71%)	8 / 66 (12.12%)
occurrences (all)	6	3	9
Abdominal pain upper			
subjects affected / exposed	3 / 36 (8.33%)	3 / 35 (8.57%)	3 / 66 (4.55%)
occurrences (all)	3	4	3
Constipation			

subjects affected / exposed	4 / 36 (11.11%)	1 / 35 (2.86%)	5 / 66 (7.58%)
occurrences (all)	5	1	10
Dental caries			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	5 / 36 (13.89%)	8 / 35 (22.86%)	14 / 66 (21.21%)
occurrences (all)	7	10	30
Dry mouth			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	4 / 66 (6.06%)
occurrences (all)	0	0	4
Dyspepsia			
subjects affected / exposed	2 / 36 (5.56%)	5 / 35 (14.29%)	8 / 66 (12.12%)
occurrences (all)	2	5	9
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	1 / 66 (1.52%)
occurrences (all)	1	2	1
Nausea			
subjects affected / exposed	17 / 36 (47.22%)	11 / 35 (31.43%)	34 / 66 (51.52%)
occurrences (all)	30	15	49
Toothache			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	3 / 66 (4.55%)
occurrences (all)	2	0	7
Vomiting			
subjects affected / exposed	7 / 36 (19.44%)	5 / 35 (14.29%)	21 / 66 (31.82%)
occurrences (all)	11	7	35
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 36 (5.56%)	2 / 35 (5.71%)	9 / 66 (13.64%)
occurrences (all)	2	4	11
Alopecia			
subjects affected / exposed	0 / 36 (0.00%)	3 / 35 (8.57%)	7 / 66 (10.61%)
occurrences (all)	0	3	7
Dermatitis			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	2 / 66 (3.03%)
occurrences (all)	0	2	2

Dermatitis contact			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	2 / 66 (3.03%)
occurrences (all)	2	1	2
Dry skin			
subjects affected / exposed	0 / 36 (0.00%)	3 / 35 (8.57%)	7 / 66 (10.61%)
occurrences (all)	0	3	7
Eczema			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	2 / 66 (3.03%)
occurrences (all)	1	2	2
Hirsutism			
subjects affected / exposed	4 / 36 (11.11%)	3 / 35 (8.57%)	5 / 66 (7.58%)
occurrences (all)	4	3	5
Hyperhidrosis			
subjects affected / exposed	3 / 36 (8.33%)	3 / 35 (8.57%)	3 / 66 (4.55%)
occurrences (all)	3	3	3
Onychoclasis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	5 / 36 (13.89%)	1 / 35 (2.86%)	7 / 66 (10.61%)
occurrences (all)	7	1	7
Rash			
subjects affected / exposed	8 / 36 (22.22%)	3 / 35 (8.57%)	10 / 66 (15.15%)
occurrences (all)	10	3	12
Skin hyperpigmentation			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	4 / 66 (6.06%)
occurrences (all)	2	2	5
Skin lesion			
subjects affected / exposed	3 / 36 (8.33%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences (all)	4	0	1
Urticaria			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	2 / 66 (3.03%)
occurrences (all)	2	0	2
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	1	2	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	7 / 36 (19.44%)	10 / 35 (28.57%)	17 / 66 (25.76%)
occurrences (all)	12	14	35
Glucocorticoid deficiency			
subjects affected / exposed	10 / 36 (27.78%)	9 / 35 (25.71%)	8 / 66 (12.12%)
occurrences (all)	19	16	14
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 36 (19.44%)	10 / 35 (28.57%)	12 / 66 (18.18%)
occurrences (all)	11	19	24
Back pain			
subjects affected / exposed	9 / 36 (25.00%)	13 / 35 (37.14%)	7 / 66 (10.61%)
occurrences (all)	9	15	10
Limb discomfort			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	6 / 66 (9.09%)
occurrences (all)	0	2	6
Musculoskeletal pain			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	3 / 66 (4.55%)
occurrences (all)	2	1	4
Myalgia			
subjects affected / exposed	2 / 36 (5.56%)	7 / 35 (20.00%)	11 / 66 (16.67%)
occurrences (all)	2	7	14
Neck pain			
subjects affected / exposed	2 / 36 (5.56%)	2 / 35 (5.71%)	3 / 66 (4.55%)
occurrences (all)	2	2	4
Osteoarthritis			
subjects affected / exposed	3 / 36 (8.33%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences (all)	4	0	1
Osteopenia			

subjects affected / exposed	2 / 36 (5.56%)	2 / 35 (5.71%)	1 / 66 (1.52%)
occurrences (all)	3	2	1
Osteoporosis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	2 / 36 (5.56%)	5 / 35 (14.29%)	6 / 66 (9.09%)
occurrences (all)	3	5	7
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	6 / 66 (9.09%)
occurrences (all)	1	1	6
Cystitis			
subjects affected / exposed	3 / 36 (8.33%)	2 / 35 (5.71%)	1 / 66 (1.52%)
occurrences (all)	8	2	1
Folliculitis			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	4	2	0
Fungal skin infection			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 66 (0.00%)
occurrences (all)	1	2	0
Gastroenteritis			
subjects affected / exposed	4 / 36 (11.11%)	3 / 35 (8.57%)	5 / 66 (7.58%)
occurrences (all)	4	4	7
Gastroenteritis viral			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Hordeolum			
subjects affected / exposed	0 / 36 (0.00%)	3 / 35 (8.57%)	2 / 66 (3.03%)
occurrences (all)	0	3	4
Influenza			
subjects affected / exposed	5 / 36 (13.89%)	8 / 35 (22.86%)	10 / 66 (15.15%)
occurrences (all)	7	10	19
Nasopharyngitis			
subjects affected / exposed	9 / 36 (25.00%)	11 / 35 (31.43%)	13 / 66 (19.70%)
occurrences (all)	14	26	32

Sinusitis			
subjects affected / exposed	3 / 36 (8.33%)	1 / 35 (2.86%)	4 / 66 (6.06%)
occurrences (all)	4	1	4
Tooth abscess			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	0 / 66 (0.00%)
occurrences (all)	2	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 36 (5.56%)	5 / 35 (14.29%)	7 / 66 (10.61%)
occurrences (all)	3	8	12
Urinary tract infection			
subjects affected / exposed	6 / 36 (16.67%)	4 / 35 (11.43%)	14 / 66 (21.21%)
occurrences (all)	12	11	15
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 36 (8.33%)	7 / 35 (20.00%)	11 / 66 (16.67%)
occurrences (all)	3	7	15
Hypercholesterolaemia			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	1 / 66 (1.52%)
occurrences (all)	1	2	2
Hyperglycaemia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	1 / 66 (1.52%)
occurrences (all)	4	0	2
Hypertriglyceridaemia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	2 / 66 (3.03%)
occurrences (all)	5	0	4
Hypokalaemia			
subjects affected / exposed	3 / 36 (8.33%)	3 / 35 (8.57%)	11 / 66 (16.67%)
occurrences (all)	4	5	13
Iron deficiency			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 66 (0.00%)
occurrences (all)	2	0	0
Vitamin D deficiency			
subjects affected / exposed	3 / 36 (8.33%)	1 / 35 (2.86%)	2 / 66 (3.03%)
occurrences (all)	3	1	2

Non-serious adverse events	All Patients		
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	134 / 137 (97.81%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	9 / 137 (6.57%)		
occurrences (all)	9		
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 137 (17.52%)		
occurrences (all)	31		
Hypotension			
subjects affected / exposed	13 / 137 (9.49%)		
occurrences (all)	16		
Varicose vein			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
General disorders and administration site conditions			
Application site rash			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Asthenia			
subjects affected / exposed	27 / 137 (19.71%)		
occurrences (all)	37		
Chest discomfort			
subjects affected / exposed	5 / 137 (3.65%)		
occurrences (all)	5		
Chills			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	45 / 137 (32.85%)		
occurrences (all)	67		
Gait disturbance			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Influenza like illness			

subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Malaise			
subjects affected / exposed	10 / 137 (7.30%)		
occurrences (all)	10		
Oedema			
subjects affected / exposed	9 / 137 (6.57%)		
occurrences (all)	13		
Oedema peripheral			
subjects affected / exposed	22 / 137 (16.06%)		
occurrences (all)	28		
Pain			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	20 / 137 (14.60%)		
occurrences (all)	26		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 137 (13.87%)		
occurrences (all)	21		
Dyspnoea			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	7		
Nasal congestion			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	9		
Oropharyngeal pain			

subjects affected / exposed	14 / 137 (10.22%)		
occurrences (all)	14		
Rhinitis allergic			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	7 / 137 (5.11%)		
occurrences (all)	8		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	12 / 137 (8.76%)		
occurrences (all)	14		
Depression			
subjects affected / exposed	13 / 137 (9.49%)		
occurrences (all)	17		
Insomnia			
subjects affected / exposed	13 / 137 (9.49%)		
occurrences (all)	14		
Irritability			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	7		
Panic attack			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	7 / 137 (5.11%)		
occurrences (all)	7		
Investigations			
11-deoxycortisol increased			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	6		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	5 / 137 (3.65%)		
occurrences (all)	6		
Alanine aminotransferase increased			

subjects affected / exposed	4 / 137 (2.92%)			
occurrences (all)	6			
Aspartate aminotransferase increased				
subjects affected / exposed	4 / 137 (2.92%)			
occurrences (all)	4			
Blood cholesterol increased				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	5			
Blood corticotrophin increased				
subjects affected / exposed	28 / 137 (20.44%)			
occurrences (all)	30			
Blood testosterone increased				
subjects affected / exposed	16 / 137 (11.68%)			
occurrences (all)	18			
Cortisol decreased				
subjects affected / exposed	4 / 137 (2.92%)			
occurrences (all)	6			
Cortisol free urine decreased				
subjects affected / exposed	11 / 137 (8.03%)			
occurrences (all)	13			
Cortisol free urine increased				
subjects affected / exposed	8 / 137 (5.84%)			
occurrences (all)	8			
Haemoglobin decreased				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	4			
Hormone level abnormal				
subjects affected / exposed	18 / 137 (13.14%)			
occurrences (all)	26			
Lipase increased				
subjects affected / exposed	4 / 137 (2.92%)			
occurrences (all)	5			
Low density lipoprotein increased				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	4			

Renin increased subjects affected / exposed occurrences (all)	6 / 137 (4.38%) 8		
Weight decreased subjects affected / exposed occurrences (all)	9 / 137 (6.57%) 10		
Weight increased subjects affected / exposed occurrences (all)	5 / 137 (3.65%) 5		
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	7 / 137 (5.11%) 9		
Ligament sprain subjects affected / exposed occurrences (all)	5 / 137 (3.65%) 5		
Cardiac disorders			
Bundle branch block right subjects affected / exposed occurrences (all)	2 / 137 (1.46%) 2		
Tachycardia subjects affected / exposed occurrences (all)	8 / 137 (5.84%) 8		
Nervous system disorders			
Amnesia subjects affected / exposed occurrences (all)	2 / 137 (1.46%) 2		
Carpal tunnel syndrome subjects affected / exposed occurrences (all)	3 / 137 (2.19%) 5		
Dizziness subjects affected / exposed occurrences (all)	26 / 137 (18.98%) 36		
Headache subjects affected / exposed occurrences (all)	50 / 137 (36.50%) 94		

Hypoaesthesia subjects affected / exposed occurrences (all)	9 / 137 (6.57%) 11		
Memory impairment subjects affected / exposed occurrences (all)	5 / 137 (3.65%) 5		
Migraine subjects affected / exposed occurrences (all)	5 / 137 (3.65%) 5		
Paraesthesia subjects affected / exposed occurrences (all)	5 / 137 (3.65%) 6		
Somnolence subjects affected / exposed occurrences (all)	5 / 137 (3.65%) 5		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	15 / 137 (10.95%) 20		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	3 / 137 (2.19%) 3		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	4 / 137 (2.92%) 4		
Eye pruritus subjects affected / exposed occurrences (all)	2 / 137 (1.46%) 2		
Photophobia subjects affected / exposed occurrences (all)	2 / 137 (1.46%) 3		
Vision blurred subjects affected / exposed occurrences (all)	4 / 137 (2.92%) 5		
Gastrointestinal disorders			

Abdominal distension				
subjects affected / exposed	6 / 137 (4.38%)			
occurrences (all)	10			
Abdominal pain				
subjects affected / exposed	15 / 137 (10.95%)			
occurrences (all)	18			
Abdominal pain upper				
subjects affected / exposed	9 / 137 (6.57%)			
occurrences (all)	10			
Constipation				
subjects affected / exposed	10 / 137 (7.30%)			
occurrences (all)	16			
Dental caries				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	2			
Diarrhoea				
subjects affected / exposed	27 / 137 (19.71%)			
occurrences (all)	47			
Dry mouth				
subjects affected / exposed	4 / 137 (2.92%)			
occurrences (all)	4			
Dyspepsia				
subjects affected / exposed	15 / 137 (10.95%)			
occurrences (all)	16			
Gastrooesophageal reflux disease				
subjects affected / exposed	4 / 137 (2.92%)			
occurrences (all)	4			
Nausea				
subjects affected / exposed	62 / 137 (45.26%)			
occurrences (all)	94			
Toothache				
subjects affected / exposed	5 / 137 (3.65%)			
occurrences (all)	9			
Vomiting				
subjects affected / exposed	33 / 137 (24.09%)			
occurrences (all)	53			

Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	13 / 137 (9.49%)		
occurrences (all)	17		
Alopecia			
subjects affected / exposed	10 / 137 (7.30%)		
occurrences (all)	10		
Dermatitis			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	4		
Dermatitis contact			
subjects affected / exposed	5 / 137 (3.65%)		
occurrences (all)	5		
Dry skin			
subjects affected / exposed	10 / 137 (7.30%)		
occurrences (all)	10		
Eczema			
subjects affected / exposed	5 / 137 (3.65%)		
occurrences (all)	5		
Hirsutism			
subjects affected / exposed	12 / 137 (8.76%)		
occurrences (all)	12		
Hyperhidrosis			
subjects affected / exposed	9 / 137 (6.57%)		
occurrences (all)	9		
Onychoclasis			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	13 / 137 (9.49%)		
occurrences (all)	15		
Rash			
subjects affected / exposed	21 / 137 (15.33%)		
occurrences (all)	25		
Skin hyperpigmentation			

subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	9		
Skin lesion			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	5		
Urticaria			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	4		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	34 / 137 (24.82%)		
occurrences (all)	61		
Glucocorticoid deficiency			
subjects affected / exposed	27 / 137 (19.71%)		
occurrences (all)	49		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 137 (21.17%)		
occurrences (all)	54		
Back pain			
subjects affected / exposed	29 / 137 (21.17%)		
occurrences (all)	34		
Limb discomfort			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences (all)	8		
Musculoskeletal pain			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	7		
Myalgia			

subjects affected / exposed	20 / 137 (14.60%)		
occurrences (all)	23		
Neck pain			
subjects affected / exposed	7 / 137 (5.11%)		
occurrences (all)	8		
Osteoarthritis			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	5		
Osteopenia			
subjects affected / exposed	5 / 137 (3.65%)		
occurrences (all)	6		
Osteoporosis			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	13 / 137 (9.49%)		
occurrences (all)	15		
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences (all)	8		
Cystitis			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	11		
Folliculitis			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	6		
Fungal skin infection			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	12 / 137 (8.76%)		
occurrences (all)	15		
Gastroenteritis viral			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		

Hordeolum			
subjects affected / exposed	5 / 137 (3.65%)		
occurrences (all)	7		
Influenza			
subjects affected / exposed	23 / 137 (16.79%)		
occurrences (all)	36		
Nasopharyngitis			
subjects affected / exposed	33 / 137 (24.09%)		
occurrences (all)	72		
Sinusitis			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences (all)	9		
Tooth abscess			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	14 / 137 (10.22%)		
occurrences (all)	23		
Urinary tract infection			
subjects affected / exposed	24 / 137 (17.52%)		
occurrences (all)	38		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 137 (15.33%)		
occurrences (all)	25		
Hypercholesterolaemia			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	6		
Hypertriglyceridaemia			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	9		
Hypokalaemia			

subjects affected / exposed	17 / 137 (12.41%)		
occurrences (all)	22		
Iron deficiency			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Vitamin D deficiency			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2014	Harmonization Procedure review. Changes were made to: - Revise the definition of the optional Extension Period. - Clarify the time-to-escape definition. - Revise the premature patient withdrawal criteria. - Revise QTcF based withdrawal criteria. - Revise visit evaluation schedule. - Revise electrocardiogram collection schedule.
11 March 2015	Issued when 12 patients had been treated to: - Add country-specific (China) intensive PK sampling in order to investigate potential ethnic differences in osilodrostat pharmacokinetics. - Update inclusion and exclusion criteria.
29 March 2016	Issued when 75 patients had been treated to: - Expand the description of the dose dispensation process. - Elaborate on dose adjustments and communication of dosing instructions. - Add specific criteria for the identification and management of patients with potential drug-induced liver injury.
06 July 2017	Issued when 137 patients had been treated to: - Further increase the duration of the optional Extension Period. - Provide continued access to the study drug for those patients benefitting from the treatment until a separate long-term safety follow-up study is set up at participating sites.
29 June 2018	Enrollment was completed under Amendment 4. Issued when 91 patients were ongoing to: - Increase the maximum duration of the optional extension period by one additional year. - Add the central pituitary magnetic resonance imaging/computed tomography assessment for tumor re-occurrence and tumor invasiveness.

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.

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.nov for complete trial results.

Notes: