Clinical trial results:
A Phase III, multi-center, randomized, double-blind, 48 week study with an initial 12 week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease

Summary

EudraCT number	2014-004092-23
Trial protocol	ES GR BE PL PT
Global end of trial date	31 December 2020

Results information

Result version number	v1 (current)
This version publication date	21 August 2021
First version publication date	21 August 2021

Trial information

Trial identification

Sponsor protocol code	CLCI699C2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02697734
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, 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	31 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2020
Global end of trial reached?	Yes
Global end of trial date	31 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: To demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at Week 12.

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	03 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	China: 12
Country: Number of subjects enrolled	Costa Rica: 3
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	74
EEA total number of subjects	24

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	72
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Number of subjects - enrolled: 74; analyzed: 73 (One patient was randomized but did not receive any study treatment as the patient experienced an SAE and discontinued the study)

Pre-assignment

Screening details:

Full Analysis Set: comprises all randomized participants who received at least one dose of study drug (osilodrostat or placebo).

There are 73 participants in the FAS who were randomized and received treatment.

Period 1

Period 1 title	Core phase - up to week 48
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	osilodrostat Group

Arm description:

Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration).

Arm type	Experimental
Investigational medicinal product name	Osilodrostat
Investigational medicinal product code	LCI699
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose in Period 1 was 2 mg b.i.d. osilodrostat. Osildrostat dosing regimen included up-titration following a 5 mg b.i.d., 10 mg b.i.d. and 20 mg b.i.d. escalation sequence during Period 1.

Arm title	osilodrostat Placebo Group

Arm description:

Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet for oral use

Number of subjects in period 1[1]	osilodrostat Group	osilodrostat Placebo Group
Started	48	25
Completed	42	23
Not completed	6	2
Consent withdrawn by subject	4	-
Physician decision	1	-
Adverse event, non-fatal	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 5 participants completed core phase and did not enter the optional extension phase.

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	osilodrostat Group

Arm description:

Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration).

Arm type	Experimental
Investigational medicinal product name	Osilodrostat
Investigational medicinal product code	LCI699
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In Period 2, the maximum starting dose of osilodrostat was 2 mg b.i.d., and could be <2 mg if they were receiving osilodrostat or placebo at a dose <2mg b.i.d. at the end of Period 1. Osilodrostat dosing regimen included up-titration following a 2 mg b.i.d., 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d. and 30 mg b.i.d. escalation sequence during Period 2.

Arm title	osilodrostat Placebo Group

Arm description:

Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet for oral use

Number of subjects in period 2[2]	osilodrostat Group	osilodrostat Placebo Group
Started	38	22
Completed	33	20
Not completed	5	2
Physician decision	-	1
Adverse event, non-fatal	5	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Number of subjects; enrolled: 74; analyzed: 73 (One patient was randomized but did not receive any study treatment as the patient experienced an SAE and discontinued the study)

Baseline characteristics

Reporting groups	
Reporting group title	osilodrostat Group
Reporting group description:	
Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration).	
Reporting group title	osilodrostat Placebo Group
Reporting group description:	
Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).	

Reporting group values	osilodrostat Group	osilodrostat Placebo Group	Total
Number of subjects	48	25	73
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	46	25	71
>=65 years	2	0	2
Age Continuous Units: Years			
arithmetic mean	42.3	38.9	
standard deviation	± 13.82	± 12.33	-
Sex: Female, Male Units: Participants			
Female	43	18	61
Male	5	7	12
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	9	8	17
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	0	2
White	34	15	49
More than one race	0	1	1
Unknown or Not Reported	2	1	3

Subject analysis sets	
Subject analysis set title	All participants combined
Subject analysis set type	Full analysis
Subject analysis set description:	
Consisted of all randomized participants who received at least one dose of osilodrostat.	
Subject analysis set title	All Participants
Subject analysis set type	Full analysis
Subject analysis set description:	
All Participants	
Subject analysis set title	osilodrostat Incident Dose 1mg

Subject analysis set type	Full analysis
Subject analysis set description: Participants received 1mg of osilodrostat.	
Subject analysis set title	osilodrostat Incident Dose 2mg
Subject analysis set type	Full analysis
Subject analysis set description: Participants received 2mg of osilodrostat.	
Subject analysis set title	osilodrostat Incident Dose 5mg
Subject analysis set type	Full analysis
Subject analysis set description: Participants received 5mg of osilodrostat.	

Reporting group values	All participants combined	All Participants	osilodrostat Incident Dose 1mg
Number of subjects	73	73	16
Age Categorical Units: Participants			
<=18 years Between 18 and 65 years >=65 years			
Age Continuous Units: Years arithmetic mean standard deviation	 80.8 ±	 2 ±	 ±
Sex: Female, Male Units: Participants			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	osilodrostat Incident Dose 2mg	osilodrostat Incident Dose 5mg	
Number of subjects	55	29	
Age Categorical Units: Participants			
<=18 years Between 18 and 65 years >=65 years			
Age Continuous Units: Years arithmetic mean standard deviation	 ±	 ±	

Sex: Female, Male Units: Participants			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	osilodrostat Group
Reporting group description:	
Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration).	
Reporting group title	osilodrostat Placebo Group
Reporting group description:	
Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).	
Reporting group title	osilodrostat Group
Reporting group description:	
Participants in this arm were randomized to receive the study drug, osilodrostat, followed after Week 12 by open-label osilodrostat at the starting dose (with a second dose titration).	
Reporting group title	osilodrostat Placebo Group
Reporting group description:	
Participants in this arm were randomized to receive osilodrostat placebo followed after Week 12 by open-label osilodrostat at the starting dose (with a dose titration).	
Subject analysis set title	All participants combined
Subject analysis set type	Full analysis
Subject analysis set description:	
Consisted of all randomized participants who received at least one dose of osilodrostat.	
Subject analysis set title	All Participants
Subject analysis set type	Full analysis
Subject analysis set description:	
All Participants	
Subject analysis set title	osilodrostat Incident Dose 1mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received 1mg of osilodrostat.	
Subject analysis set title	osilodrostat Incident Dose 2mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received 2mg of osilodrostat.	
Subject analysis set title	osilodrostat Incident Dose 5mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received 5mg of osilodrostat.	

Primary: Percentage of randomized participants with a complete response

End point title	Percentage of randomized participants with a complete response
End point description:	
A complete responder at week 12 is defined as a participant who had a mean urine free cortisol ≤ upper limit of normal (mUFC ≤ ULN) at Week 12. Participants who had a missing mUFC assessment at Week 12 were counted as non-responders for the primary endpoint.	
End point type	Primary
End point timeframe:	
at Week 12	

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Participants	37	2		

Statistical analyses

Statistical analysis title	osilodrostat Group v osilodrostat Placebo Group
Comparison groups	osilodrostat Group v osilodrostat Placebo Group
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	43.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.06
upper limit	343.19

Secondary: Time-to-first control of mUFC - number (%) of participants with mUFC <=ULN

End point title	Time-to-first control of mUFC - number (%) of participants with mUFC <=ULN

End point description:

To assess time-to-first control of mUFC, (in days) from randomization to the first mUFC collection that was ≤ ULN before completion/discontinuation of placebo-controlled period.
Participants who did not achieve post-baseline mUFC control were censored at discontinuation or completion of placebo-controlled period, whichever was earlier.

End point type	Secondary

End point timeframe:

up to 12 weeks

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Participants	45	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-first control of mUFC - median time to first controlled mUFC response

End point title	Time-to-first control of mUFC - median time to first controlled mUFC response

End point description:

To assess time-to-first control of mUFC, (in days) from randomization to the first mUFC collection that was ≤ ULN before completion/discontinuation of placebo-controlled period.

Participants who did not achieve post-baseline mUFC control were censored at discontinuation or completion of placebo-controlled period, whichever was earlier.

The median time-to-first control and corresponding two-sided 95% Confidence Interval were calculated using Kaplan-Meier methodology of Brookmeyer and Crowley (1982).

End point type	Secondary

End point timeframe:

up to 12 weeks

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Days				
number (confidence interval 95%)	35 (34.0 to 52.0)	999 (87.0 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-first control of mUFC - % event probability estimates

End point title	Time-to-first control of mUFC - % event probability estimates

End point description:

To assess time-to-first control of mUFC, (in days) from randomization to the first mUFC collection that was ≤ ULN before completion/discontinuation of placebo-controlled period.

Participants who did not achieve post-baseline mUFC control were censored at discontinuation or completion of placebo-controlled period, whichever was earlier.

% Event probability estimate is the estimated probability that a participant will have an event prior to

the specified time point. % Event probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment
groups; Greenwood formula is used for Confidence Interval (CI) of Kaplan-Meier (KM) estimates.

End point type	Secondary

End point timeframe:

up to 12 weeks

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Percentage				
number (confidence interval 95%)				
2 Weeks	25.0 (15.0 to 39.8)	16.0 (6.3 to 37.2)		
5 Weeks	60.4 (47.0 to 74.1)	20.0 (8.9 to 41.6)		
8 Weeks	79.4 (67.0 to 89.4)	28.0 (14.5 to 49.9)		
12 Weeks	999 (999 to 999)	28.0 (14.5 to 49.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-escape during osilodrostat treatment from collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN - number (%) of participants

End point title	Time-to-escape during osilodrostat treatment from collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN - number (%) of participants

End point description:

To assess time-to-escape from the first collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN on two consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons. Escape will not be assessed for participants during the first 26 weeks.

End point type	Secondary

End point timeframe:

up to 48 weeks

End point values	osilodrostat Group	osilodrostat Placebo Group	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	48	25	73	
Units: Participants	0	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-escape during osilodrostat treatment from collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN - median time to escape from normal mUFC

End point title	Time-to-escape during osilodrostat treatment from collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN - median time to escape from normal mUFC

End point description:

To assess time-to-escape from the first collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN on two consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons. Escape will not be assessed for participants during the first 26 weeks.

The median time-to-escape and corresponding two-sided 95% Confidence Interval were calculated using Kaplan-Meier methodology of Brookmeyer and Crowley (1982).

End point type	Secondary

End point timeframe:

from week 26 to week 48

End point values	osilodrostat Group	osilodrostat Placebo Group	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	48	25	73	
Units: days				
number (confidence interval 95%)	999 (999 to 999)	999 (116.0 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-escape during osilodrostat treatment from collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN - % event probability estimates

End point title	Time-to-escape during osilodrostat treatment from collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN - % event probability estimates

End point description:

To assess time-to-escape from the first collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN on two consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons. Escape will not be assessed for participants during the first 26 weeks.

% Event probability estimate is the estimated probability that a participant will have an event prior to the specified time point.
% Event probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CI of KM estimates.

End point type	Secondary

End point timeframe:

week 26 to week 36

End point values	osilodrostat Group	osilodrostat Placebo Group	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	48	25	73	
Units: Percentage				
number (confidence interval 95%)				
26 Weeks	0 (0 to 0)	21.3 (5.7 to 61.9)	15.6 (4.1 to 49.6)	
36 Weeks	0 (0 to 0)	999 (999 to 999)	15.6 (4.1 to 49.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with a complete response (mUFC ≤ ULN) or a partial response (mUFC decrease ≥ 50% from baseline and >ULN) at week 12, 36 and 48

End point title	Patients with a complete response (mUFC ≤ ULN) or a partial response (mUFC decrease ≥ 50% from baseline and >ULN) at week 12, 36 and 48

End point description:

Overall response rate defined as percentage of complete responders (mUFC ≤ ULN) plus partial responders (≥ 50% reduction in mUFC from baseline and >ULN) at week 12, 36, 48 by treatment arms for all patients.

End point type	Secondary

End point timeframe:

baseline, week 12, 36 and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Participants				
week 12 Complete responders	37	2		
week 12 Partial responders	2	2		
week 12 Overall responders (complete or partial)	39	4		
week 12 Non-responders	9	21		
week 36 Complete responders	38	21		

week 36 Partial responders	2	3		
week 36 Overall responders (complete or partial	40	24		
week 36 Non-responders	8	1		
week 48 Complete responders	34	16		
week 48 Partial responders	5	3		
week 48 Overall responders (complete or partial	39	19		
week 48 Non-responders	9	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 12, Week 36, and Week 48 in clinical signs of Cushing's disease

End point title	Change from baseline to Week 12, Week 36, and Week 48 in clinical signs of Cushing's disease

End point description:

Change from baseline to Week 12, Week 36, and Week 48 in each of the following clinical signs of Cushing's disease, captured by: a semi-quantitative Likert scale for facial rubor, striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises) by randomized treatment arm. The number/proportion of participants with an improvement or no change compared to baseline are reported

End point type	Secondary

End point timeframe:

baseline, Week 12, Week 36 and Week 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Participants				
Facial Rubor - week 12 (n=42,20)	36	19		
Hirsutism - week 12 (n=36,16)	34	15		
Striae - week 12 (n=41,20)	38	19		
Supraclavicular Fat Pad - week 12 (n=42,21)	41	19		
Dorsal Fat Pad - week 12 (n=41,21)	35	17		
Proximal Muscle Atrophy - week 12 (n=42,21)	38	20		
Central Obesity - week 12 (n=42,21)	37	21		
Ecchymoses - week 12 (n=42,20)	39	19		
Facial Rubor - week 36 (n=41,23)	39	22		
Hirsutism - week 36 (n=34,17)	28	16		
Striae - week 36 (n=40,23)	38	23		
Supraclavicular Fat Pad - week 36 (n=41,24)	40	24		
Dorsal Fat Pad - week 36 (n=40,24)	36	22		

Proximal Muscle Atrophy - week 36 (n=41,23)	37	22		
Central Obesity - week 36 (n=41,24)	37	21		
Ecchymoses - week 36 (n=41,23)	39	22		
Facial Rubor - week 48 (n=39,21)	37	21		
Hirsutism - week 48 (n=33,15)	29	15		
Striae - week 48 (n=38,21)	38	21		
Supraclavicular Fat Pad - week 48 (n=39,22)	38	22		
Dorsal Fat Pad - week 48 (n=38,22)	36	20		
Proximal Muscle Atrophy - week 48 (n=39,22)	35	21		
Central Obesity - week 48 (n=39,22)	35	21		
Ecchymoses - week 48 (n=39,21)	38	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EQ-5D-5L Utility Index

End point title	Change from baseline in EQ-5D-5L Utility Index

End point description:

EQ-5D-5L Utility Index:
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. 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 utility index can be computed from the EQ 5D-5L descriptive system with utility scores ranging from -0.281 (worst imaginable health state) to 1 (best imaginable health state), with -0.281 representing an "unconscious" health state. A single index value is analyzed for the EQ-5D-5L score. An increase from baseline in the EQ-ED-5L utility index is indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Actual - baseline (n=48,24)	0.825 (± 0.1486)	0.903 (± 0.1125)		
Actual Change from Baseline at Week 12 (n=46,24)	-0.000 (± 0.1402)	0.021 (± 0.0771)		
Actual Change from Baseline at Week 48 (n=42,22)	0.044 (± 0.1393)	0.033 (± 0.0826)		
Actual Change from Week 12 at Week 36 (n=44,23)	0.025 (± 0.1283)	0.010 (± 0.0487)		
Actual Change from Week 36 at Week 48 (n=42,22)	0.023 (± 0.0762)	-0.008 (± 0.0367)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EQ-5D VAS

End point title	Change from baseline in EQ-5D VAS

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Actual - baseline (n=48,23)	70.3 (± 17.26)	76.7 (± 17.88)		
Actual Change from Baseline at week 12 (n=46,24)	0.5 (± 13.57)	-0.3 (± 10.52)		
Actual Change from Baseline at week 48 (n=42,22)	9.4 (± 13.13)	5.8 (± 9.45)		
Actual Change from Week 12 at Week 36 (n=44,23)	6.0 (± 11.08)	3.7 (± 9.29)		
Actual Change from Week 36 at Week 48 (n=42,22)	3.2 (± 8.40)	-0.8 (± 4.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Beck Depression Inventory-II - Total Score Derived

End point title	Change from baseline in Beck Depression Inventory-II - Total Score Derived

End point description:

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. A global score ranges from 0 to 63 and is calculated with a higher score representing a

greater level of depression. The following scoring guidelines for interpretation of BDI-II have been suggested (Smarr, 2011): Minimal range =0-13, Mild depression =14-19, Moderate depression =20-28 and Severe depression = 29-63. A reduction from baseline in BDI-II is indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Actual - baseline (n=48,25)	12.2 (± 10.22)	8.4 (± 7.82)		
Actual Change from Baseline at Week 12 (n=46,24)	-1.4 (± 7.99)	-3.9 (± 5.42)		
Actual Change from Baseline at Week 48 (n=42,22)	-4.3 (± 7.52)	-4.0 (± 7.70)		
Actual Change from Week 12 at Week 36 (n=44,23)	-2.0 (± 4.70)	0.6 (± 6.29)		
Actual Change from Week 36 at Week 48 (n=42,22)	-1.1 (± 4.83)	-0.4 (± 3.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma osilodrostat concentrations (ng/mL)

End point title	Plasma osilodrostat concentrations (ng/mL)

End point description:

Plasma osilodrostat concentrations (ng/mL)

End point type	Secondary

End point timeframe:

pre-dose and 1-2hrs post dose at weeks 1, 2, 5, 8, 12, 14, 20, 26

End point values	osilodrostat Incident Dose 1mg	osilodrostat Incident Dose 2mg	osilodrostat Incident Dose 5mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	55	29	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
week 1 1-2 hrs post dose (n=1,43,0)	3.85 (± 999)	7.29 (± 101.0)	999 (± 999)	
week 2 0 hrs pre dose (n=0,41,0)	999 (± 999)	2.19 (± 107.5)	999 (± 999)	
week 2 1-2 hrs post dose (n=0,42,0)	999 (± 999)	9.76 (± 53.4)	999 (± 999)	

week 5 pre dose (n=2,18,17)	0.576 (± 141.9)	2.07 (± 82.1)	5.06 (± 109.6)	
week 5 1-2 hrs post dose (n=2,9,29)	3.64 (± 60.5)	11.1 (± 31.5)	25.8 (± 84.4)	
week 8 0 hrs pre dose (n=2,4,13)	0.971 (± 76.7)	2.64 (± 53.7)	4.99 (± 55.6)	
week 8 1-2 hrs post dose (n=3,6,14)	3.70 (± 47.6)	8.31 (± 45.6)	23.3 (± 68.1)	
week 12 0 hrs pre dose (n=2,8,11)	1.55 (± 3.7)	2.45 (± 39.2)	5.03 (± 74.6)	
week 12 1-2 hrs post dose (n=4,34,0)	4.93 (± 32.0)	11.7 (± 78.9)	999 (± 999)	
week 14 0 hrs pre dose (n=4,55,0)	0.974 (± 129.7)	1.96 (± 74.9)	999 (± 999)	
week 14 1-2 hrs post dose (n=6,49,6)	3.74 (± 161.4)	9.69 (± 35.8)	22.6 (± 37.8)	
week 20 0 hrs pre dose (n=10,19,15)	1.63 (± 71.1)	1.95 (± 68.1)	6.21 (± 74.3)	
week 20 1-2 hrs post dose (n=13,18,12)	6.09 (± 27.3)	8.66 (± 94.0)	26.0 (± 99.3)	
week 26 0 hrs pre dose (n=12,13,10)	1.77 (± 86.4)	2.12 (± 77.8)	6.89 (± 85.1)	
week 26 1-2 hrs post dose (n=16,14,10)	5.28 (± 31.5)	8.04 (± 50.7)	33.1 (± 31.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with mUFC ≤ ULN at week 36

End point title	Percentage of participants with mUFC ≤ ULN at week 36

End point description:

The complete response rate in both arms combined at Week 36. A complete responder at Week 36 is defined as a participant who had mean urine free cortisol <= upper limit of normal (mUFC <= ULN) at Week 36. Participants with missing mUFC at Week 36 were counted as non-responders.

End point type	Secondary

End point timeframe:

At Week 36

End point values	All participants combined			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: Percentage of participants				
number (confidence interval 95%)	80.8 (69.9 to 89.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mUFC

End point title	Change from baseline in mUFC

End point description:

To assess the change in mean urinary free cortisol (mUFC) from baseline by treatment arm.

End point type	Secondary

End point timeframe:

Baseline, weeks 2,5,8,12,14,17,20,23,26,29,32,36,40,48,60,72,84,96

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: nmol/24hr				
arithmetic mean (standard deviation)				
actual - baseline	421.4 (± 291.25)	451.5 (± 535.09)		
change from baseline at week 2 (n=47,24)	-139.3 (± 404.45)	164.9 (± 543.82)		
change from baseline at week 5 (n=46,25)	-252.8 (± 338.48)	-37.3 (± 280.84)		
change from baseline at week 8 (n=44,25)	-330.2 (± 303.35)	-35.0 (± 325.30)		
change from baseline at week 12 (n=44,24)	-332.7 (± 315.50)	-49.1 (± 332.29)		
change from baseline at week 14 (n=45,25)	-191.7 (± 446.77)	-209.5 (± 407.62)		
change from baseline at week 17 (n=45,25)	-238.8 (± 362.46)	-284.5 (± 557.47)		
change from baseline at week 20 (n=44,24)	-294.5 (± 316.65)	-355.1 (± 538.96)		
change from baseline at week 23 (n=44,25)	-314.1 (± 307.60)	-387.8 (± 466.15)		
change from baseline at week 26 (n=43,25)	-345.2 (± 306.35)	-365.4 (± 458.28)		
change from baseline at week 29 (n=43,25)	-331.4 (± 299.63)	-391.4 (± 534.57)		
change from baseline at week 32 (n=44,25)	-341.3 (± 298.96)	-298.0 (± 655.52)		
change from baseline at week 36 (n=43,25)	-349.6 (± 310.46)	-372.9 (± 519.17)		
change from baseline at week 40 (n=43,23)	-333.4 (± 307.63)	-364.7 (± 542.28)		
change from baseline at week 48 (n=42,22)	-325.1 (± 314.30)	-367.5 (± 554.16)		
change from baseline at week 60 (n=33,19)	-364.4 (± 339.57)	-335.2 (± 571.06)		
change from baseline at week 72 (n=31,17)	-381.2 (± 338.68)	-372.4 (± 624.69)		
change from baseline at week 84 (n=23,17)	-398.6 (± 377.81)	-196.0 (± 916.83)		
change from baseline at week 96 (n=6,7)	-414.5 (± 347.83)	-616.4 (± 881.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bone mineral density (BMD) by Dual-energy X-ray absorptiometry (DXA) scan at the femoral neck, hip and spinal cord - QC corrected

End point title	Change from baseline in bone mineral density (BMD) by Dual-energy X-ray absorptiometry (DXA) scan at the femoral neck, hip and spinal cord - QC corrected

End point description:

The change from baseline in bone mineral density at the femoral neck, hip and spinal cord at Week 48 by treatment arm - QC corrected. An increase in bone mineral density is indicative of an improvement. CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, week 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: g/cm2				
arithmetic mean (standard deviation)				
FEMORAL NECK QC CORRECTED- b/l - (n=43,24)	0.8 (± 0.16)	0.8 (± 0.14)		
FEMORAL NECK QC CORR - week 48 - CFB (n=28,19)	0.0 (± 0.04)	0.0 (± 0.03)		
HIP QC CORRECTED - b/l - (n=43,24)	0.9 (± 0.14)	0.9 (± 0.11)		
HIP QC CORRECTED - week 48 - CFB (n=28,19)	0.0 (± 0.03)	0.0 (± 0.02)		
SPINAL CORD QC CORRECTED - b/l (n=42,23)	1.0 (± 0.15)	1.0 (± 0.18)		
SPINAL CORD QC CORRECTED - week 48 - CFB (n=28,18)	0.0 (± 0.04)	0.0 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bone mineral density (BMD) T-score by Dual-energy X-ray absorptiometry (DXA) scan at the femoral neck, hip and spinal cord - QC corrected

End point title	Change from baseline in bone mineral density (BMD) T-score by Dual-energy X-ray absorptiometry (DXA) scan at the femoral neck, hip and spinal cord - QC corrected

End point description:

The change from baseline in bone mineral density at the femoral neck, hip and spinal cord at Week 48 by treatment arm - QC corrected. An increase in bone mineral density is indicative of an improvement. T-score is the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient. The WHO criteria are: Normal is a T-score of −1.0 or higher". CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, week 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: scores on a scale				
arithmetic mean (standard deviation)				
FEMORAL NECK QC CORRECTED - b/l (n=43,24)	-1.2 (± 1.06)	-1.3 (± 0.89)		
FEMORAL NECK QC CORRECTED - CFB at wk 48 (n=28,19)	0.1 (± 0.30)	0.1 (± 0.21)		
HIP QC CORRECTED - b/l - Actual (n=43,24)	-0.7 (± 1.08)	-0.8 (± 0.84)		
HIP QC CORRECTED - CFB at wk 48 (n=28,19)	0.0 (± 0.27)	0.0 (± 0.16)		
SPINAL CORD QC CORRECTED - baseline - (n=42,23)	-1.2 (± 1.10)	-1.1 (± 1.40)		
SPINAL CORD QC CORRECTED - CFB at wk 48 (n=28,18)	0.1 (± 0.32)	0.1 (± 0.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose

End point title	Change in fasting plasma glucose

End point description:

Change from baseline in fasting plasma glucose at Week 12, Week 36, and Week 48 by treatment arm. CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mg/dL				
arithmetic mean (standard deviation)				
Fasting glucose (mg/dL) - baseline - (n=47,24)	97.3 (± 18.14)	91.4 (± 15.15)		
Fasting glucose (mg/dL) - CFB at week 12 (n=44,23)	-4.3 (± 14.84)	-1.7 (± 10.59)		
Fasting glucose (mg/dL) - CFB at week 36 (n=43,24)	-6.7 (± 12.48)	-1.1 (± 12.93)		

Fasting glucose (mg/dL) - CFB at week 48 (n=41,21)	-5.6 (± 14.13)	1.8 (± 13.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hemoglobin A1C

End point title	Change in Hemoglobin A1C

End point description:

Change from baseline in Hemoglobin A1C (%) at Week 12, Week 36, and Week 48 by treatment arm. CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: percentage of Hemoglobin A1C				
arithmetic mean (standard deviation)				
Hemoglobin A1C (%) - baseline	6.0 (± 0.92)	5.7 (± 0.56)		
Hemoglobin A1C (%) - CFB at week 12 (n=46,24)	-0.2 (± 0.44)	0.0 (± 0.27)		
Hemoglobin A1C (%) CFB at week 36 (n=44,25)	-0.2 (± 0.54)	-0.1 (± 0.46)		
Hemoglobin A1C (%) CFB at week 48 (n=41,21)	-0.2 (± 0.58)	0.1 (± 0.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cholesterol

End point title	Change in Cholesterol

End point description:

Change from baseline in Cholesterol (mmol/L) at Week 12, Week 36, and Week 48 by treatment arm. CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mmol/L				
arithmetic mean (standard deviation)				
Cholesterol (mmol/L) - baseline (n=45,25)	5.7 (± 1.30)	5.3 (± 1.15)		
Cholesterol (mmol/L) - CFB at week 12 (n=44,24)	-0.8 (± 0.95)	0.0 (± 0.65)		
Cholesterol (mmol/L) - CFB at week 36 (n=44,25)	-1.0 (± 1.28)	-0.4 (± 0.89)		
Cholesterol (mmol/L) - CFB at week 48 (n=42,22)	-0.6 (± 1.36)	-0.4 (± 1.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LDL Cholesterol

End point title	Change in LDL Cholesterol

End point description:

Change from baseline in LDL Cholesterol (mmol/L) at Week 12, Week 36, and Week 48 by treatment arm.
CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mmol/L				
arithmetic mean (standard deviation)				
LDL Cholesterol (mmol/L) - baseline (n=45,24)	3.4 (± 1.12)	3.0 (± 1.07)		
LDL Cholesterol (mmol/L) - CBF at wk 12 (n=44,23)	-0.5 (± 0.80)	0.1 (± 0.47)		
LDL Cholesterol (mmol/L) - CFB at wk 36 (n=44,24)	-0.6 (± 1.08)	-0.2 (± 0.70)		
LDL Cholesterol (mmol/L) - CFB at wk 48 (n=41,21)	-0.5 (± 0.99)	-0.2 (± 0.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HDL Cholesterol

End point title	Change in HDL Cholesterol

End point description:

Change from baseline in HDL Cholesterol (mmol/L) at Week 12, Week 36, and Week 48 by treatment arm.
CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mmol/L				
arithmetic mean (standard deviation)				
HDL Cholesterol (mmol/L) - baseline (n=45,25)	1.6 (± 0.35)	1.5 (± 0.38)		
HDL Cholesterol (mmol/L)-CFB at week 12 (n=44,24)	-0.3 (± 0.29)	0.0 (± 0.28)		
HDL Cholesterol (mmol/L)-CFB at week 36 (n=44,25)	-0.3 (± 0.27)	-0.2 (± 0.25)		
HDL Cholesterol (mmol/L)-CFB at week 48 (n=42,22)	-0.2 (± 0.27)	-0.1 (± 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Triglyceride

End point title	Change in Triglyceride

End point description:

Change from baseline in Triglyceride (mmol/L) at Week 12, Week 36, and Week 48 by treatment arm.
CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mmol/L				
arithmetic mean (standard deviation)				
Triglyceride (mmol/L)- baseline (n=45,25)	1.5 (± 0.79)	1.7 (± 0.85)		
Triglyceride (mmol/L)-CFB at week 12(n=44,24)	0.0 (± 0.53)	-0.2 (± 0.54)		
Triglyceride (mmol/L)-CFB at week 36 (n=44,25)	-0.1 (± 0.55)	-0.1 (± 0.71)		
Triglyceride (mmol/L)-CFB at week 48 (n=42,22)	0.1 (± 0.92)	-0.2 (± 0.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Standing Systolic Blood Pressure

End point title	Change in Standing Systolic Blood Pressure

End point description:

Change from baseline in Standing Systolic Blood Pressure (mmHg) at Week 12, Week 36, and Week 48 by treatment arm.
CFB = change from baseline
BP = blood pressure

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mmHg				
arithmetic mean (standard deviation)				
Standing Systolic Blood Pressure -b/l (n=46,25)	132.4 (± 19.16)	130.0 (± 17.72)		
Standing Systolic BP - CFB at week 12 (n=44,24)	-7.1 (± 18.08)	-0.9 (± 11.77)		
Standing Systolic BP - CFB at week 36 (n=42,25)	-9.3 (± 19.09)	-7.0 (± 21.04)		
Standing Systolic BP - CFB at week 48 (n=41,22)	-9.1 (± 19.45)	-11.0 (± 22.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Supine Systolic Blood Pressure

End point title	Change in Supine Systolic Blood Pressure

End point description:

Change from baseline in Supine Systolic Blood Pressure (mmHg) at Week 12, Week 36, and Week 48 by treatment arm.
CFB = change from baseline
BP = blood pressure

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mmHg				
arithmetic mean (standard deviation)				
Supine Systolic BP - baseline (n=48,25)	131.7 (± 18.33)	127.8 (± 18.69)		
Supine Systolic BP - CFB at week 12 (n=46,24)	-8.0 (± 17.54)	2.3 (± 15.91)		
Supine Systolic BP - CFB at week 36 (n=42,25)	-9.7 (± 19.88)	-4.4 (± 17.43)		
Supine Systolic BP - CFB at week 48 (n=42,22)	-7.4 (± 19.38)	-7.5 (± 18.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Standing Diastolic Blood Pressure

End point title	Change in Standing Diastolic Blood Pressure

End point description:

Change from baseline in Standing Diastolic Blood Pressure (mmHg) at Week 12, Week 36, and Week 48 by treatment arm.
CFB = change from baseline
BP = blood pressure

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mmHg				
arithmetic mean (standard deviation)				
Standing Diastolic BP - baseline (n=46,25)	87.2 (± 12.74)	88.2 (± 10.83)		
Standing Diastolic BP - CFB at week 12 (n=44,24)	-4.8 (± 11.14)	-1.4 (± 9.84)		
Standing Diastolic BP - CFB at week 36 (n=42,25)	-6.0 (± 12.09)	-4.4 (± 13.98)		
Standing Diastolic BP - CFB at week 48 (n=41,22)	-4.4 (± 11.64)	-3.9 (± 13.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Supine Diastolic Blood Pressure

End point title	Change in Supine Diastolic Blood Pressure

End point description:

Change from baseline in Supine Diastolic Blood Pressure (mmHg) at Week 12, Week 36, and Week 48 by treatment arm.
CFB = change from baseline
BP = blood pressure

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: mmHg				
arithmetic mean (standard deviation)				
Supine Diastolic BP - baseline (n=48,25)	83.9 (± 11.71)	81.4 (± 11.21)		
Supine Diastolic BP - CFB at week 12 (n=46,24)	-6.3 (± 11.05)	-0.1 (± 8.31)		
Supine Diastolic BP - CFB at week 36 (n=44,25)	-7.7 (± 11.92)	-3.4 (± 11.37)		
Supine Diastolic BP - CFB at week 48 (n=41,22)	-5.8 (± 11.60)	-3.7 (± 10.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Weight

End point title	Change in Weight

End point description:

Change from baseline in Weight (kg) at Week 12, Week 36, and Week 48 by treatment arm

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: kg				
arithmetic mean (standard deviation)				
Weight - baseline (n=48,25)	78.8 (± 17.46)	77.3 (± 16.90)		
Weight - change from baseline at wk 12(n=46,24)	-0.8 (± 3.09)	-0.1 (± 2.12)		
Weight - change from baseline at wk 36 (n=44,25)	-3.0 (± 5.53)	-4.8 (± 5.63)		
Weight - change from baseline at wk 48 (n=42,22)	-3.6 (± 6.53)	-5.5 (± 6.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Waist Circumference

End point title	Change in Waist Circumference

End point description:

Change from baseline in Waist Circumference (cm) at Week 12, Week 36, and Week 48 by treatment arm.
CFB = change from baseline

End point type	Secondary

End point timeframe:

Baseline, weeks 12, 36, and 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: cm				
arithmetic mean (standard deviation)				

Waist Circumference - baseline (n=48,25)	102.5 (± 17.01)	103.4 (± 15.52)		
Waist Circumference- CFB at week 12 (n=46,24)	-1.0 (± 4.43)	-0.5 (± 3.35)		
Waist Circumference- CFB at week 36 (n=44,25)	-3.9 (± 6.36)	-2.1 (± 8.60)		
Waist Circumference - CFB at week 48 (n=42,22)	-4.1 (± 6.10)	-5.3 (± 5.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Standardized Health Related Quality of Life score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

End point title	Change from baseline in Standardized Health Related Quality of Life score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

End point description:

The CushingQoL is a valid and reliable disease-specific QoL questionnaire which assesses health-related quality of life (HRQoL) in patients with Cushing's syndrome and has been validated in patients with Cushing's disease. The CushingQoL consists of questions reflecting dimensions of HRQoL related to physical aspects (e.g. 'I bruise easily'), psychological aspects (e.g. 'I am more irritable, I have sudden mood swings and angry outbursts'), and social aspects (e.g. 'I have had to give up my social or leisure activities due to my illness').

The questionnaire consists of 12 items measured on a five point Likert-type scale assessing how often or how much each item has been related to the patient's Cushing's disease in the previous week. The raw score is calculated by summing the individual item scores prior to being standardized so that the total score ranges from 0 to 100. Increases from baseline are indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Actual - Baseline (n=48,25)	49.1 (± 19.60)	56.9 (± 18.99)		
Actual Change from Baseline at Week 12 (n=46,24)	6.2 (± 14.85)	8.6 (± 12.06)		
Actual Change from Baseline at Week 48 (n=42,22)	11.7 (± 16.30)	12.8 (± 14.24)		
Actual Change from Week 12 at Week 36 (n=44,23)	4.7 (± 9.01)	-0.5 (± 9.99)		
Actual Change from Week 36 at Week 48 (n=42,22)	0.1 (± 8.43)	2.5 (± 7.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Standardized Psychosocial issues score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

End point title	Change from baseline in Standardized Psychosocial issues score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

End point description:

The CushingQoL is a valid and reliable disease-specific QoL questionnaire which assesses health-related quality of life (HRQoL) in patients with Cushing's syndrome and has been validated in patients with Cushing's disease. The CushingQoL consists of questions reflecting dimensions of HRQoL related to physical aspects (e.g. 'I bruise easily'), psychological aspects (e.g. 'I am more irritable, I have sudden mood swings and angry outbursts'), and social aspects (e.g. 'I have had to give up my social or leisure activities due to my illness').

The questionnaire consists of 12 items measured on a five point Likert-type scale assessing how often or how much each item has been related to the patient's Cushing's disease in the previous week. The raw score is calculated by summing the individual item scores prior to being standardized so that the total score ranges from 0 to 100. Increases from baseline are indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Actual - baseline (n=48,25)	49.9 (± 20.34)	56.7 (± 21.11)		
Actual Change from Baseline at Week 12 (n=46,24)	6.1 (± 17.21)	9.6 (± 13.61)		
Actual Change from Baseline at Week 48 (n=42,22)	11.1 (± 17.84)	13.0 (± 16.30)		
Actual Change from Week 12 at Week 36 (n=44,23)	4.1 (± 9.94)	-1.3 (± 12.36)		
Actual Change from Week 36 at Week 48 (n=42,22)	0.1 (± 9.60)	2.4 (± 8.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Standardized Physical problems score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

End point title	Change from baseline in Standardized Physical problems score, using Cushing Disease-specific Quality of Life Patient Reported Outcome (PRO) Assessment

End point description:

The CushingQoL is a valid and reliable disease-specific QoL questionnaire which assesses health-related quality of life (HRQoL) in patients with Cushing's syndrome and has been validated in patients with Cushing's disease. The CushingQoL consists of questions reflecting dimensions of HRQoL related to physical aspects (e.g. 'I bruise easily'), psychological aspects (e.g. 'I am more irritable, I have sudden mood swings and angry outbursts'), and social aspects (e.g. 'I have had to give up my social or leisure activities due to my illness').

The questionnaire consists of 12 items measured on a five point Likert-type scale assessing how often or how much each item has been related to the patient's Cushing's disease in the previous week. The raw score is calculated by summing the individual item scores prior to being standardized so that the total score ranges from 0 to 100. Increases from baseline are indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 12 and 48, Week 12 to Week 36, Week 36 to Week 48.

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Actual - baseline (n=48,25)	46.9 (± 22.32)	57.7 (± 21.91)		
Actual Change from Baseline at Week 12 (n=46,24)	6.3 (± 13.29)	5.6 (± 13.38)		
Actual Change from Baseline at Week 48 (n=42,22)	13.3 (± 19.83)	12.1 (± 15.59)		
Actual Change from Week 12 at Week 36 (n=44,23)	6.6 (± 12.40)	2.2 (± 12.11)		
Actual Change from Week 36 at Week 48 (n=42,22)	23.59 (± 11.27)	2.7 (± 12.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in serum cortisol

End point title	Change from baseline in serum cortisol

End point description:

Change from baseline in serum cortisol

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, Week 48

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: nmol/L				
arithmetic mean (standard deviation)				
Baseline - actual (n=47,25)	565.8 (± 169.01)	486.1 (± 198.12)		
Actual Change from Baseline at Week 12 (n=44,24)	-276.0 (± 178.43)	73.0 (± 185.29)		
Actual Change from Baseline at Week 36 (n=42,25)	-267.0 (± 174.18)	-157.8 (± 225.56)		
Actual Change from Baseline at Week 48 (n=41,22)	-210.7 (± 161.07)	-131.0 (± 236.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in late night saliva cortisol

End point title	Change from baseline in late night saliva cortisol
End point description:	
Change from baseline in late night saliva cortisol (nmol/L)	
End point type	Secondary
End point timeframe:	
Baseline, Week 12, Week 36, Week 48	

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: nmol/L				
arithmetic mean (standard deviation)				
Baseline - actual (n=48,25)	11.7 (± 28.68)	9.0 (± 6.74)		
Actual Change from Baseline at Week 12 (n=46,24)	-8.5 (± 29.60)	1.3 (± 8.87)		
Actual Change from Baseline at Week 36 (n=42,25)	-9.6 (± 30.82)	-5.8 (± 6.84)		
Actual Change from Baseline at Week 48 (n=41,22)	-9.3 (± 29.05)	-5.0 (± 5.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in morning saliva cortisol

End point title	Change from baseline in morning saliva cortisol
End point description:	
Change from baseline in morning saliva cortisol (nmol/L)	
End point type	Secondary
End point timeframe:	
Baseline, Week 12, Week 36, Week 48	

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: nmol/L				
arithmetic mean (standard deviation)				
Baseline - actual (n=48,25)	17.2 (± 30.00)	14.1 (± 12.29)		
Actual Change from Baseline at Week 12 (n=46,24)	-11.6 (± 30.05)	-0.3 (± 11.21)		
Actual Change from Baseline at Week 36 (n=40,25)	-11.8 (± 30.74)	-9.3 (± 11.82)		
Actual Change from Baseline at Week 48 (n=41,22)	-11.8 (± 31.74)	-6.0 (± 10.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in hair cortisol levels

End point title	Change from baseline in hair cortisol levels
End point description:	
Change from baseline in hair cortisol levels	
End point type	Secondary
End point timeframe:	
Baseline, Week 26, Week 48	

End point values	osilodrostat Group	osilodrostat Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	25		
Units: pg/mg				
arithmetic mean (standard deviation)				
Baseline - actual (n=19,9)	38.9 (± 37.48)	10.5 (± 10.47)		
Actual Change from Baseline at Week 26 (n=16,7)	-15.8 (± 32.83)	-1.1 (± 12.72)		

Actual Change from Baseline at Week 48 (n=14,6)	-17.8 (± 26.66)	-9.7 (± 8.90)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from first dose of study treatment until end of study treatment plus 8 weeks post treatment, up to maximum duration of 116.7 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo controlled period@ Osilodrostat arm

Reporting group description:

Placebo controlled period@ Osilodrostat arm

Reporting group title	Placebo controlled period@ Placebo arm

Reporting group description:

Placebo controlled period@ Placebo arm

Reporting group title	Overall study period@ Osilodrostat@(Osilodrostat arm)

Reporting group description:

Overall study period@ Osilodrostat@(Osilodrostat arm)

Reporting group title	Overall study period@ Osilodrostat@(Placebo arm)

Reporting group description:

Overall study period@ Osilodrostat@(Placebo arm)

Reporting group title	Overall study period@ All Patients

Reporting group description:

Overall study period@ All Patients

Serious adverse events	Placebo controlled period@ Osilodrostat arm	Placebo controlled period@ Placebo arm	Overall study period@ Osilodrostat@(Osilodrostat arm)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 48 (4.17%)	1 / 25 (4.00%)	10 / 48 (20.83%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave inversion			

subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Conjunctival laceration			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral vascular occlusion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
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	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive duodenitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
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			
Dyspnoea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Obstructive airways disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
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	0 / 48 (0.00%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
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			
Anal abscess			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	0 / 48 (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
Pyelonephritis			

subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 48 (2.08%)
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	Overall study period@ Osilodrostat@(Placebo arm)	Overall study period@ All Patients	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	10 / 73 (13.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Conjunctival laceration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal injury			

subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral vascular occlusion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erosive duodenitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 25 (0.00%)	3 / 73 (4.11%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			

subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo controlled period@ Osilodrostat arm	Placebo controlled period@ Placebo arm	Overall study period@ Osilodrostat@(Osilodrostat arm)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 48 (93.75%)	21 / 25 (84.00%)	47 / 48 (97.92%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 48 (14.58%)	7 / 25 (28.00%)	12 / 48 (25.00%)
occurrences (all)	7	7	18
Hypotension			
subjects affected / exposed	5 / 48 (10.42%)	0 / 25 (0.00%)	9 / 48 (18.75%)
occurrences (all)	5	0	10
Orthostatic hypotension			
subjects affected / exposed	4 / 48 (8.33%)	0 / 25 (0.00%)	7 / 48 (14.58%)
occurrences (all)	4	0	8
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	11 / 48 (22.92%)	0 / 25 (0.00%)	15 / 48 (31.25%)
occurrences (all)	11	0	18
Fatigue			
subjects affected / exposed	12 / 48 (25.00%)	4 / 25 (16.00%)	23 / 48 (47.92%)
occurrences (all)	13	4	36
Oedema peripheral			
subjects affected / exposed	5 / 48 (10.42%)	0 / 25 (0.00%)	12 / 48 (25.00%)
occurrences (all)	6	0	13
Pyrexia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	5 / 48 (10.42%)
occurrences (all)	2	0	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	4 / 48 (8.33%)
occurrences (all)	0	0	4
Dyspnoea			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	2 / 48 (4.17%)
occurrences (all)	1	0	2
Epistaxis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	1	0	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 48 (4.17%)	2 / 25 (8.00%)	3 / 48 (6.25%)
occurrences (all)	2	2	3
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	2 / 48 (4.17%)
occurrences (all)	1	0	2

Blood cholesterol increased			
subjects affected / exposed	2 / 48 (4.17%)	1 / 25 (4.00%)	3 / 48 (6.25%)
occurrences (all)	2	1	8
Blood potassium decreased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 25 (4.00%)	2 / 48 (4.17%)
occurrences (all)	1	1	2
Blood pressure increased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 25 (4.00%)	3 / 48 (6.25%)
occurrences (all)	1	1	3
Blood testosterone increased			
subjects affected / exposed	5 / 48 (10.42%)	0 / 25 (0.00%)	13 / 48 (27.08%)
occurrences (all)	5	0	13
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Renin increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	1 / 48 (2.08%)
occurrences (all)	1	0	1
Weight decreased			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	2	0	3
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	4 / 48 (8.33%)
occurrences (all)	2	0	4
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 48 (0.00%)	2 / 25 (8.00%)	2 / 48 (4.17%)
occurrences (all)	0	2	2
Tachycardia			
subjects affected / exposed	6 / 48 (12.50%)	0 / 25 (0.00%)	8 / 48 (16.67%)
occurrences (all)	6	0	8
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 48 (18.75%)	4 / 25 (16.00%)	19 / 48 (39.58%)
occurrences (all)	12	4	25

Paraesthesia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	4 / 48 (8.33%)
occurrences (all)	0	0	4
Headache			
subjects affected / exposed	7 / 48 (14.58%)	6 / 25 (24.00%)	17 / 48 (35.42%)
occurrences (all)	8	8	27
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 25 (8.00%)	2 / 48 (4.17%)
occurrences (all)	2	2	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 48 (6.25%)	1 / 25 (4.00%)	4 / 48 (8.33%)
occurrences (all)	3	1	4
Abdominal pain			
subjects affected / exposed	4 / 48 (8.33%)	0 / 25 (0.00%)	10 / 48 (20.83%)
occurrences (all)	4	0	11
Abdominal pain upper			
subjects affected / exposed	1 / 48 (2.08%)	1 / 25 (4.00%)	3 / 48 (6.25%)
occurrences (all)	1	1	3
Diarrhoea			
subjects affected / exposed	10 / 48 (20.83%)	0 / 25 (0.00%)	14 / 48 (29.17%)
occurrences (all)	11	0	20
Nausea			
subjects affected / exposed	15 / 48 (31.25%)	3 / 25 (12.00%)	22 / 48 (45.83%)
occurrences (all)	21	5	40
Vomiting			
subjects affected / exposed	5 / 48 (10.42%)	0 / 25 (0.00%)	9 / 48 (18.75%)
occurrences (all)	5	0	9
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	9 / 48 (18.75%)
occurrences (all)	3	0	11
Alopecia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 25 (4.00%)	4 / 48 (8.33%)
occurrences (all)	1	1	7
Dry skin			

subjects affected / exposed	3 / 48 (6.25%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	3	0	6
Eczema			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	3
Pruritus			
subjects affected / exposed	6 / 48 (12.50%)	0 / 25 (0.00%)	7 / 48 (14.58%)
occurrences (all)	6	0	11
Hirsutism			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	6 / 48 (12.50%)
occurrences (all)	0	1	6
Skin hyperpigmentation			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	2	0	5
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	7 / 48 (14.58%)	0 / 25 (0.00%)	12 / 48 (25.00%)
occurrences (all)	8	0	18
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 48 (35.42%)	3 / 25 (12.00%)	26 / 48 (54.17%)
occurrences (all)	20	3	48
Back pain			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	8 / 48 (16.67%)
occurrences (all)	2	0	9
Muscle spasms			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	2	0	4
Muscular weakness			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	4 / 48 (8.33%)
occurrences (all)	2	0	5
Myalgia			

subjects affected / exposed	10 / 48 (20.83%)	1 / 25 (4.00%)	15 / 48 (31.25%)
occurrences (all)	11	2	26
Pain in extremity			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	2	0	3
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	4 / 48 (8.33%)
occurrences (all)	1	0	5
Influenza			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	4 / 48 (8.33%)
occurrences (all)	2	0	8
Laryngitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	1 / 48 (2.08%)	1 / 25 (4.00%)	2 / 48 (4.17%)
occurrences (all)	2	1	4
Oral herpes			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	1	0	3
Pharyngitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	5 / 48 (10.42%)
occurrences (all)	1	0	6
Upper respiratory tract infection			
subjects affected / exposed	5 / 48 (10.42%)	0 / 25 (0.00%)	12 / 48 (25.00%)
occurrences (all)	5	0	20
Urinary tract infection			
subjects affected / exposed	4 / 48 (8.33%)	0 / 25 (0.00%)	8 / 48 (16.67%)
occurrences (all)	4	0	12
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 48 (37.50%)	4 / 25 (16.00%)	24 / 48 (50.00%)
occurrences (all)	21	4	37
Hypercholesterolaemia			

subjects affected / exposed	3 / 48 (6.25%)	1 / 25 (4.00%)	6 / 48 (12.50%)
occurrences (all)	3	1	6
Hypoglycaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	3 / 48 (6.25%)
occurrences (all)	1	0	3
Hypokalaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	6 / 48 (12.50%)
occurrences (all)	1	0	9

Non-serious adverse events	Overall study period@ Osilodrostat@(Placebo arm)	Overall study period@ All Patients	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)	71 / 73 (97.26%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 25 (16.00%)	16 / 73 (21.92%)	
occurrences (all)	10	28	
Hypotension			
subjects affected / exposed	3 / 25 (12.00%)	12 / 73 (16.44%)	
occurrences (all)	4	14	
Orthostatic hypotension			
subjects affected / exposed	1 / 25 (4.00%)	8 / 73 (10.96%)	
occurrences (all)	1	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 25 (8.00%)	17 / 73 (23.29%)	
occurrences (all)	2	20	
Fatigue			
subjects affected / exposed	6 / 25 (24.00%)	29 / 73 (39.73%)	
occurrences (all)	10	46	
Oedema peripheral			
subjects affected / exposed	0 / 25 (0.00%)	12 / 73 (16.44%)	
occurrences (all)	0	13	
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	5 / 73 (6.85%)	
occurrences (all)	0	5	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 25 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	4	
Dyspnoea			
subjects affected / exposed	2 / 25 (8.00%)	4 / 73 (5.48%)	
occurrences (all)	2	4	
Epistaxis			
subjects affected / exposed	2 / 25 (8.00%)	2 / 73 (2.74%)	
occurrences (all)	2	2	
Nasal congestion			
subjects affected / exposed	0 / 25 (0.00%)	3 / 73 (4.11%)	
occurrences (all)	0	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 25 (8.00%)	4 / 73 (5.48%)	
occurrences (all)	3	5	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 25 (12.00%)	6 / 73 (8.22%)	
occurrences (all)	3	6	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 25 (12.00%)	5 / 73 (6.85%)	
occurrences (all)	4	6	
Blood cholesterol increased			
subjects affected / exposed	0 / 25 (0.00%)	3 / 73 (4.11%)	
occurrences (all)	0	8	
Blood potassium decreased			
subjects affected / exposed	2 / 25 (8.00%)	4 / 73 (5.48%)	
occurrences (all)	3	5	
Blood pressure increased			
subjects affected / exposed	0 / 25 (0.00%)	3 / 73 (4.11%)	
occurrences (all)	0	3	
Blood testosterone increased			
subjects affected / exposed	5 / 25 (20.00%)	18 / 73 (24.66%)	
occurrences (all)	6	19	

Electrocardiogram T wave inversion			
subjects affected / exposed	2 / 25 (8.00%)	2 / 73 (2.74%)	
occurrences (all)	2	2	
Renin increased			
subjects affected / exposed	4 / 25 (16.00%)	5 / 73 (6.85%)	
occurrences (all)	4	5	
Weight decreased			
subjects affected / exposed	1 / 25 (4.00%)	4 / 73 (5.48%)	
occurrences (all)	1	4	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 25 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	4	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 25 (0.00%)	2 / 73 (2.74%)	
occurrences (all)	0	2	
Tachycardia			
subjects affected / exposed	1 / 25 (4.00%)	9 / 73 (12.33%)	
occurrences (all)	3	11	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 25 (12.00%)	22 / 73 (30.14%)	
occurrences (all)	3	28	
Paraesthesia			
subjects affected / exposed	0 / 25 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	4	
Headache			
subjects affected / exposed	8 / 25 (32.00%)	25 / 73 (34.25%)	
occurrences (all)	13	40	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 73 (4.11%)	
occurrences (all)	1	3	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 25 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	4	
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	12 / 73 (16.44%)	
occurrences (all)	9	20	
Abdominal pain upper			
subjects affected / exposed	0 / 25 (0.00%)	3 / 73 (4.11%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	3 / 25 (12.00%)	17 / 73 (23.29%)	
occurrences (all)	4	24	
Nausea			
subjects affected / exposed	5 / 25 (20.00%)	27 / 73 (36.99%)	
occurrences (all)	7	47	
Vomiting			
subjects affected / exposed	0 / 25 (0.00%)	9 / 73 (12.33%)	
occurrences (all)	0	9	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 25 (4.00%)	10 / 73 (13.70%)	
occurrences (all)	1	12	
Alopecia			
subjects affected / exposed	1 / 25 (4.00%)	5 / 73 (6.85%)	
occurrences (all)	1	8	
Dry skin			
subjects affected / exposed	1 / 25 (4.00%)	4 / 73 (5.48%)	
occurrences (all)	1	7	
Eczema			
subjects affected / exposed	2 / 25 (8.00%)	4 / 73 (5.48%)	
occurrences (all)	2	5	
Pruritus			
subjects affected / exposed	2 / 25 (8.00%)	9 / 73 (12.33%)	
occurrences (all)	2	13	
Hirsutism			

subjects affected / exposed	1 / 25 (4.00%)	7 / 73 (9.59%)	
occurrences (all)	1	7	
Skin hyperpigmentation			
subjects affected / exposed	1 / 25 (4.00%)	4 / 73 (5.48%)	
occurrences (all)	1	6	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	2 / 25 (8.00%)	2 / 73 (2.74%)	
occurrences (all)	3	3	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	6 / 25 (24.00%)	18 / 73 (24.66%)	
occurrences (all)	9	27	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 25 (28.00%)	33 / 73 (45.21%)	
occurrences (all)	8	56	
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	10 / 73 (13.70%)	
occurrences (all)	3	12	
Muscle spasms			
subjects affected / exposed	1 / 25 (4.00%)	4 / 73 (5.48%)	
occurrences (all)	1	5	
Muscular weakness			
subjects affected / exposed	2 / 25 (8.00%)	6 / 73 (8.22%)	
occurrences (all)	6	11	
Myalgia			
subjects affected / exposed	3 / 25 (12.00%)	18 / 73 (24.66%)	
occurrences (all)	4	30	
Pain in extremity			
subjects affected / exposed	2 / 25 (8.00%)	5 / 73 (6.85%)	
occurrences (all)	2	5	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	5	

Influenza			
subjects affected / exposed	0 / 25 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	8	
Laryngitis			
subjects affected / exposed	0 / 25 (0.00%)	3 / 73 (4.11%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	4 / 73 (5.48%)	
occurrences (all)	2	6	
Oral herpes			
subjects affected / exposed	0 / 25 (0.00%)	3 / 73 (4.11%)	
occurrences (all)	0	3	
Pharyngitis			
subjects affected / exposed	1 / 25 (4.00%)	6 / 73 (8.22%)	
occurrences (all)	1	7	
Upper respiratory tract infection			
subjects affected / exposed	4 / 25 (16.00%)	16 / 73 (21.92%)	
occurrences (all)	4	24	
Urinary tract infection			
subjects affected / exposed	4 / 25 (16.00%)	12 / 73 (16.44%)	
occurrences (all)	5	17	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 25 (40.00%)	34 / 73 (46.58%)	
occurrences (all)	11	48	
Hypercholesterolaemia			
subjects affected / exposed	0 / 25 (0.00%)	6 / 73 (8.22%)	
occurrences (all)	0	6	
Hypoglycaemia			
subjects affected / exposed	1 / 25 (4.00%)	4 / 73 (5.48%)	
occurrences (all)	1	4	
Hypokalaemia			
subjects affected / exposed	2 / 25 (8.00%)	8 / 73 (10.96%)	
occurrences (all)	3	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2017	- Issued when 18 patients had been enrolled in the study. The following key changes were made: - The list of prohibited medications was revised to remove "all drugs known to prolong QT". The list of prohibited medications known to cause TdP, or with a possible risk to cause TdP, was reduced. This was based on evidence from the thorough QT study CLCI699C2105. - The risks section was updated to include neutropenia. - The duration of the optional extension period was increased in order to collect additional long-term safety and efficacy data and allow continued access to the study drug as required. - Secondary objective endpoints were added: change from baseline in serum, salivary and hair cortisol levels, actual and percentage change in biomarkers of hypercortisolism.
20 December 2019	Issued when all patients had been enrolled. The following key changes were made: - Changed the end of study definition - Removed Beck Depression Inventory (BDI) from Appendix 3 as Beck's Depression Inventory was not used in the study. For this study, the BDI-II was used - Appendix 3 (Patient Quality of Life questionnaires) removed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported