Clinical trial results:
A proof-of-concept (PoC), open-label, forced titration, multi-center study to assess the safety/tolerability and efficacy of 10-weeks treatment of LCI699 followed by a 12-week treatment period in patients with Cushing' s disease.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd. com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2010-022403-22
Trial protocol	IT
Global end of trial date	22 October 2019

Results information

Result version number	v1 (current)
This version publication date	06 November 2020
First version publication date	06 November 2020

Trial information

Trial identification

Sponsor protocol code	CLCI699C2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01331239
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	22 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of 10-week treatment osilodrostat on 24 hour urine free cortisol (UFC) in patients with Cushing’s disease

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	23 March 2011
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	France: 9
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	27
EEA total number of subjects	15

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)	27
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

27 were enrolled in the study: 12 in Part l and 19 in Part ll Core. Four of the participants in the Part II Core were previously enrolled in the Part I Core.

Pre-assignment

Screening details:

For overall study: 27 patients were planned; For Part l of the study, 12 - 15 patients were planned to be enrolled. For Part ll Core 19 patients were planned to be enrolled.

Period 1

Period 1 title	Part I: Core Study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part l: Core cohort

Arm description:

Participants took an ascending dose of LCI699 (osilodrostat) from 2mg bid or 5 mg bid, up to 30 mg bid and participated in Part l of this study. 4 patients in this cohort moved to Part II of the study

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

Dosage and administration details:

Starting dose of 2 mg b.i.d increasing to 50 mg b.i.d as detailed above.

Number of subjects in period 1[1]	Part l: Core cohort
Started	12
Completed	12

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: In this period there were fewer subjects were enrolled than in the whole study. More subjects joined in the next period.

Period 2

Period 2 title	Part II: Core Study
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Part II Core: Expansion cohort

Arm description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part ll Core Expansion of this study. These patients were all newly enrolled into the phase ll part of the study.

Arm type	Experimental
Investigational medicinal product name	osilodrostat
Investigational medicinal product code	LCI699
Other name	
Pharmaceutical forms	Capsule, soft, Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients started the sequential dose- escalation treatment period at 2 mg bid of osilodrostat, or 5 mg bid if their UFC was greater than 3xULN on Day 1. This schedule of events continued every 2 weeks (i.e. Day 28, 42, 56) with potential interim dose escalation visits (on Days 35, 49, 63) during the dose escalation period, with the dose of LCI699 increasing. If at any time, the patient's UFC was less than ULN, dose escalation was to be halted and the patient remained on the current, efficacious dose through Week 10, with continued monitoring of UFC responses every 2 weeks to allow dose adjustments if necessary. If at any time the patient experienced side effects, which were either intolerable or met dose adjustment criteria, the prescribed dose was to be adjusted. The capsule formulation of osilodrostat was later changed to tablets and this change was implemented in the study with Protocol amendment 06.

Arm title	Part ll Core: Follow-up cohort

Arm description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part ll Core Follow-up of this study. These patients were patients who transferred from Part l Core phase of the study.

Arm type	Experimental
Investigational medicinal product name	osilodrostat
Investigational medicinal product code	LCI699
Other name	
Pharmaceutical forms	Capsule, soft, Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to start at the penultimate osilodrostat dose that was efficacious and well tolerated during their previous treatment, with the possibility to up- titrate the dose within 1 week based on tolerability. The capsule formulation of osilodrostat was later changed to tablets and this change was implemented in the study with Protocol amendment 06.

Number of subjects in period 2	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort
Started	15	4
Completed	7	3
Not completed	8	1
Consent withdrawn by subject	2	-
Adverse event, non-fatal	3	-
Administrative problems	1	-
Subj's cond. no longer require treatment	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Part l: Core cohort
Reporting group description:	
Participants took an ascending dose of LCI699 (osilodrostat) from 2mg bid or 5 mg bid, up to 30 mg bid and participated in Part l of this study. 4 patients in this cohort moved to Part II of the study	

Reporting group values	Part l: Core cohort	Total	
Number of subjects	12	12	
Age Categorical Units: years			
18 - 64 years	12	12	
>65 years	0	0	
Sex: Female, Male Units: Participants			
Female	8	8	
Male	4	4	
Race/Ethnicity, Customized Units: Subjects			
White	12	12	
Black or African American	0	0	
Asian	0	0	

Subject analysis sets	
Subject analysis set title	2mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 2mg of osilodrostat	
Subject analysis set title	5mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 5mg of osilodrostat	
Subject analysis set title	10mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 10mg of osilodrostat	
Subject analysis set title	20mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 20mg of osilodrostat	
Subject analysis set title	30mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 30mg of osilodrostat	
Subject analysis set title	2mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 2mg of osilodrostat

Subject analysis set title	5mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 5mg of osilodrostat

Subject analysis set title	10mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 10mg of osilodrostat

Subject analysis set title	20mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 20mg of osilodrostat

Subject analysis set title	2mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 2mg of osilodrostat

Subject analysis set title	5mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 5mg of osilodrostat

Subject analysis set title	Phase ll Core: Expansion cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part ll Core Expansion of this study. These patients were all newly enrolled into the phase ll part of the study.

Reporting group values	2mg bid	5mg bid	10mg bid
Number of subjects	4	13	6
Age Categorical Units: years			
18 - 64 years >65 years			
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Black or African American Asian			

Reporting group values	20mg bid	30mg bid	2mg bid
Number of subjects	1	1	6
Age Categorical Units: years			
18 - 64 years >65 years			

Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Black or African American Asian			

Reporting group values	5mg bid	10mg bid	20mg bid
Number of subjects	14	8	2
Age Categorical Units: years			
18 - 64 years >65 years			
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Black or African American Asian			

Reporting group values	2mg bid	5mg bid	Phase ll Core: Expansion cohort
Number of subjects	2	11	15
Age Categorical Units: years			
18 - 64 years >65 years			15
Sex: Female, Male Units: Participants			
Female Male			11 4
Race/Ethnicity, Customized Units: Subjects			
White Black or African American Asian			11 3 1

End points

End points reporting groups

Reporting group title	Part I: Core cohort
Reporting group description:	
Participants took an ascending dose of LCI699 (osilodrostat) from 2mg bid or 5 mg bid, up to 30 mg bid and participated in Part I of this study. 4 patients in this cohort moved to Part II of the study	
Reporting group title	Part II Core: Expansion cohort
Reporting group description:	
Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Expansion of this study. These patients were all newly enrolled into the phase II part of the study.	
Reporting group title	Part II Core: Follow-up cohort
Reporting group description:	
Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Follow-up of this study. These patients were patients who transferred from Part I Core phase of the study.	
Subject analysis set title	2mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 2mg of osilodrostat	
Subject analysis set title	5mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 5mg of osilodrostat	
Subject analysis set title	10mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 10mg of osilodrostat	
Subject analysis set title	20mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 20mg of osilodrostat	
Subject analysis set title	30mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 30mg of osilodrostat	
Subject analysis set title	2mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 2mg of osilodrostat	
Subject analysis set title	5mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 5mg of osilodrostat	
Subject analysis set title	10mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Expansion cohort who took 10mg of osilodrostat	
Subject analysis set title	20mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 20mg of osilodrostat

Subject analysis set title	2mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 2mg of osilodrostat

Subject analysis set title	5mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Expansion cohort who took 5mg of osilodrostat

Subject analysis set title	Phase ll Core: Expansion cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part ll Core Expansion of this study. These patients were all newly enrolled into the phase ll part of the study.

Primary: Percentage of responders to LCI699 based on the change in mean urinary free cortisol (UFC) from baseline to Week 10

End point title	Percentage of responders to LCI699 based on the change in mean urinary free cortisol (UFC) from baseline to Week 10[1]

End point description:

A patient was considered to be a responder if his/her mean UFC level from the three 24-hour urine samples collected at Week 10 was ≤ ULN (as defined by the local laboratories) or represented a ≥50% decrease from baseline. Patients who discontinued for a disease or treatment related reason (e.g. death, adverse event, clinical disease progression etc.), or whose mean Week 10 24-hour UFC levels were higher than the normal limit and experienced <50% decrease in UFC were classified as non-responders.

End point type	Primary

End point timeframe:

10 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint

End point values	Part l: Core cohort			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of participants				
number (not applicable)	100.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: 11-Deoxycorticosterone (Overall)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: 11- Deoxycorticosterone (Overall)

End point description:

Change in Deoxycorticosterone over time.

End point type	Secondary
End point timeframe: baseline, Week 22, Week 70, Last observed value (LOV)	

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: pmol/L				
arithmetic mean (standard deviation)				
BL: 11-Deoxycorticosterone (n =12, 4)	292.8 (± 371.54)	188.0 (± 105.21)		
WK 22: 11-Deoxycorticosterone (n= 10, 4)	6957.8 (± 9627.77)	3670.0 (± 2734.34)		
WK 70: 11-Deoxycorticosterone (n= 7, 4)	2523.1 (± 1597.39)	1743.0 (± 1048.22)		
LOV: 11-Deoxycorticosterone (n=12, 4)	1640.8 (± 2097.16)	1822.3 (± 1452.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: 11-Deoxycortisol (Overall)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: 11-Deoxycortisol (Overall)
End point description: Change in Deoxycortisol over time.	
End point type	Secondary
End point timeframe: baseline, Week 22, Week 70, Last observed value (LOV)	

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: nmol/L				
arithmetic mean (standard deviation)				
BL: 11-Deoxycortisol (n= 14, 4)	4.21 (± 4.648)	5.48 (± 6.549)		
WK 22: 11-Deoxycortisol (n= 12, 4)	45.48 (± 44.880)	54.75 (± 60.676)		
WK 70: 11-Deoxycortisol (n= 9, 4)	15.32 (± 13.463)	9.03 (± 7.934)		

LOV: 11-Deoxycortisol	8.60 (± 18.910)	11.83 (± 19.101)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Aldosterone, Thyroxine, free (T4)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Aldosterone, Thyroxine, free (T4)
End point description: Change in aldosterone & thyroxine, free over time.	
End point type	Secondary
End point timeframe: baseline, Week 22, Week 70, Last observed value (LOV)	

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: pmol/L				
arithmetic mean (standard deviation)				
BL: Aldosterone (n = 14, 4)	165.5 (± 255.07)	127.0 (± 177.04)		
WK 22: Aldosterone (n =12, 4)	-151.1 (± 290.53)	-64.5 (± 247.93)		
WK 70: Aldosterone (n = 9, 4)	-101.9 (± 153.82)	-120.0 (± 182.11)		
LOV: Aldosterone (n =14, 4)	-135.1 (± 258.36)	-99.5 (± 149.06)		
BL: Thyroxine, free (n = 14, 4)	14.02 (± 3.233)	18.40 (± 8.050)		
WK 22: Thyroxine, free (n =11, 4)	-1.17 (± 3.254)	-3.63 (± 3.247)		
WK 70: Thyroxine, free (n = 9, 4)	0.46 (± 2.355)	-3.78 (± 7.951)		
LOV: Thyroxine, free (n =14, 4)	1.69 (± 3.281)	-2.33 (± 5.324)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Estradiol (Female)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Estradiol (Female)

End point description:

Change in Estradiol in females over time.

End point type	Secondary

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: pmol/L				
arithmetic mean (standard deviation)				
BL: Female Estradiol (n =10, 3)	209.60 (± 282.423)	307.23 (± 263.028)		
WK 22: Female Estradiol (n =8, 3)	-42.19 (± 223.444)	-24.63 (± 234.288)		
WK 70: Female Estradiol (n =6, 3)	10.55 (± 187.443)	-141.00 (± 376.080)		
LOV: Female Estradiol (n =10, 3)	-114.24 (± 305.334)	666.93 (± 1108.794)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Estradiol (Male)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Estradiol (Male)

End point description:

Change in Estradiol in males over time.

End point type	Secondary

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: pmol/L				
arithmetic mean (standard deviation)				
BL: Male Estradiol	55.00 (± 25.755)	77.10 (± 999)		

WK 22: Male Estradiol	35.00 (± 68.005)	18.30 (± 999)		
WK 70: Male Estradiol (n =3, 1)	-1.00 (± 16.523)	110.10 (± 999)		
LOV: Male Estradiol	2.50 (± 55.729)	-33.10 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Follicle Stimulation Hormone (FSH) (Female)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Follicle Stimulation Hormone (FSH) (Female)
End point description: Change in FSH in females over time.	
End point type	Secondary
End point timeframe: baseline, Week 22, Week 70, Last observed value (LOV)	

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: U/L				
arithmetic mean (standard deviation)				
BL: Female FSH (n =10, 3)	9.09 (± 13.277)	2.43 (± 0.929)		
WK 22: Female FSH (n =7, 3)	14.89 (± 28.673)	2.90 (± 2.476)		
WK 70: Female FSH (n =6, 3)	3.58 (± 14.021)	3.20 (± 2.081)		
LOV: Female FSH (n =10, 3)	15.41 (± 23.613)	3.70 (± 2.524)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Follicle Stimulation Hormone (Male)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Follicle Stimulation Hormone (Male)
End point description: Change in FSH in males over time.	
End point type	Secondary

End point timeframe:
baseline, Week 22, Week 70, Last observed value (LOV)

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: U/L				
arithmetic mean (standard deviation)				
BL: Male FSH	5.88 (± 3.241)	5.80 (± 999)		
WK 22: Male FSH	-1.20 (± 1.560)	-5.20 (± 999)		
WK 70: Male FSH (n =3, 1)	-1.80 (± 1.735)	-5.80 (± 999)		
LOV: Male FSH	-1.38 (± 5.660)	-2.90 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Renin, Insulin, Tyrotropin

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Renin, Insulin, Tyrotropin

End point description:
Change in Renin, Insulin & Tyrotropin over time.

End point type	Secondary

End point timeframe:
baseline, Week 22, Week 70, Last observed value (LOV)

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: mU/L				
arithmetic mean (standard deviation)				
BL: Renin (n =14, 4)	23.706 (± 18.0642)	73.973 (± 102.338)		
WK 22: Renin (n= 12, 4)	45.899 (± 144.9575)	-16.838 (± 145.6609)		
WK 70: Renin (n= 9, 4)	70.051 (± 117.9931)	-55.638 (± 88.9155)		
LOV: Renin (n=14, 4)	24.209 (± 52.0438)	-43.718 (± 70.5958)		

BL: Insulin (n =14, 4)	25.61 (± 27.166)	22.38 (± 7.071)		
WK 22: Insulin (n= 12, 4)	-10.63 (± 20.247)	-8.58 (± 4.456)		
WK 70: Insulin (n= 9, 4)	-8.69 (± 24.132)	-12.53 (± 8.772)		
LOV: Insulin (n=14, 4)	-8.11 (± 23.169)	-5.78 (± 11.771)		
BL: Thyrotropin (n =14, 4)	0.659 (± 0.6827)	0.815 (± 0.8364)		
WK 22: Thyrotropin(n= 11, 3)	1.445 (± 2.3295)	0.280 (± 0.3118)		
WK 70: Thyrotropin (n= 9, 4)	2.387 (± 4.0991)	0.395 (± 0.4674)		
LOV: Thyrotropin (n=14, 4)	1.244 (± 3.4627)	0.885 (± 0.5994)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Insulin-like Growth Factor-1

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Insulin-like Growth Factor-1
End point description: Change in Insulin-like Growth Factor-1 over time.	
End point type	Secondary
End point timeframe: baseline, Week 22, Week 70, Last observed value (LOV)	

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: ug/L				
arithmetic mean (standard deviation)				
BL: Insulin-like Growth Factor-1 (n =14, 3)	157.56 (± 109.044)	235.30 (± 110.249)		
WK 22: Insulin-like Growth Factor-1 (n =12, 3)	-9.78 (± 67.387)	-35.20 (± 153.817)		
WK 70: Insulin-like Growth Factor-1 (n= 9, 3)	-41.23 (± 76.969)	-113.43 (± 86.529)		
LOV: Insulin-like Growth Factor-1 (n=14, 3)	-56.76 (± 105.936)	-46.07 (± 62.155)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Luteinising Hormone (LH) (Female)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Luteinising Hormone (LH) (Female)

End point description:

Change in LH in females over time.

End point type	Secondary

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: U/L				
arithmetic mean (standard deviation)				
BL: Female LH (n =10, 3)	2.78 (± 2.220)	1.00 (± 1.000)		
WK 22: Female LH (n =8, 2)	7.45 (± 17.051)	4.40 (± 0.990)		
WK 70: Female LH (n =6, 3)	7.47 (± 15.267)	2.63 (± 3.235)		
LOV: Female LH (n =10, 3)	7.30 (± 10.885)	3.37 (± 2.060)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: LH (Male)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: LH (Male)

End point description:

Change in LH in males over time.

End point type	Secondary

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: U/L				
arithmetic mean (standard deviation)				
BL: Male LH	2.48 (± 1.328)	5.90 (± 999)		
WK 22: Male LH	0.48 (± 1.081)	-5.70 (± 999)		
WK 70: Male LH (n =3, 1)	-0.53 (± 1.021)	-5.90 (± 999)		
LOV: Male LH	-0.05 (± 2.610)	-2.70 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Testosterone (Female)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Testosterone (Female)

End point description:

Change in Testosterone in females over time.

End point type	Secondary

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: nmol/L				
arithmetic mean (standard deviation)				
BL: Female Testosterone (n = 10, 3)	1.18 (± 0.820)	1.43 (± 0.404)		
WK 22: Female Testosterone (n= 8, 3)	1.85 (± 1.790)	5.27 (± 5.353)		
WK 70: Female Testosterone (n= 6, 3)	0.53 (± 1.409)	0.50 (± 1.400)		
LOV: Female Testosterone (n=10, 3)	0.25 (± 1.532)	0.17 (± 1.266)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Change from baseline (BL) in steroid hormones of HPA-axis: Testosterone (Male)

End point title	Actual Change from baseline (BL) in steroid hormones of HPA-axis: Testosterone (Male)

End point description:

Change in Testosterone in males over time.

End point type	Secondary

End point timeframe:

baseline, Week 22, Week 70, Last observed value (LOV)

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: nmol/L				
arithmetic mean (standard deviation)				
BL: Male Testosterone (n = 3, 1)	7.53 (± 4.076)	7.10 (± 999)		
WK 22: Male Testosterone (n= 4, 1)	6.55 (± 4.751)	2.40 (± 999)		
WK 70: Male Testosterone (n= 3, 1)	5.17 (± 1.504)	32.60 (± 999)		
LOV: Male Testosterone (n=4, 1)	8.15 (± 7.859)	0.00 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Fasting glucose

End point title	Actual change from BL in Cardiovascular and other metabolic parameters: Fasting glucose

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: mg/dL				
arithmetic mean (standard deviation)				
BL	108.1 (± 55.12)	96.3 (± 14.43)		
WK 22 (n = 13, 4)	-14.5 (± 32.45)	-16.3 (± 14.93)		

WK 70 (n = 10, 4) LOV	-22.5 (± 36.87) -17.9 (± 35.99)	-20.8 (± 24.62) -13.8 (± 22.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Hemoglobin A1C

End point title	Actual change from BL in Cardiovascular and other metabolic parameters: Hemoglobin A1C

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

End point values	Part II Core: Expansion cohort	Part II Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Percentage				
arithmetic mean (standard deviation)				
BL (n =13, 4)	5.7 (± 0.77)	6.0 (± 0.61)		
WK 22 (n = 11, 4)	-0.1 (± 0.27)	-0.3 (± 0.28)		
WK 70 (n = 8, 4)	-0.1 (± 0.43)	-0.6 (± 0.74)		
LOV (n = 11, 4)	-0.1 (± 0.56)	-0.4 (± 0.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Cholesterol, LDL Cholesterol, HDL Cholesterol, Triglycerides

End point title	Actual change from BL in Cardiovascular and other metabolic parameters: Cholesterol, LDL Cholesterol, HDL Cholesterol, Triglycerides

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: mmo1/L				
arithmetic mean (standard deviation)				
BL Cholesterol (n =15, 4)	5.2 (± 1.36)	5.7 (± 1.44)		
WK 22 Cholesterol (n = 13, 4)	-0.7 (± 1.58)	-0.5 (± 0.56)		
WK 70 Cholesterol (n = 10, 4)	-0.1 (± 1.35)	-1.2 (± 1.74)		
LOV Cholesterol (n = 15, 4)	0.5 (± 2.39)	1.5 (± 5.22)		
BL LDL Cholesterol (n =15, 4)	3.0 (± 1.32)	4.8 (± 2.31)		
WK 22 LDL Cholesterol (n = 13, 4)	-0.3 (± 1.35)	-1.5 (± 1.98)		
WK 70 LDL Cholesterol (n = 10, 4)	0.0 (± 1.17)	-2.2 (± 2.11)		
LOV LDL Cholesterol (n = 15, 4)	0.3 (± 1.58)	-0.7 (± 1.83)		
BL HDL Cholesterol (n = 15, 4)	1.6 (± 0.39)	2.1 (± 1.85)		
WK 22 HDL Cholesterol (n = 13, 4)	-0.3 (± 0.32)	-0.9 (± 1.58)		
WK 70 HDL Cholesterol (n = 10, 4)	-0.3 (± 0.42)	-0.9 (± 1.60)		
LOV HDL Cholesterol (n = 15, 4)	0.1 (± 0.66)	-0.0 (± 0.49)		
BL Triglycerides (n = 15, 4)	1.5 (± 0.70)	1.4 (± 0.32)		
WK 22 Triglycerides (n = 13, 4)	-0.1 (± 0.42)	0.1 (± 0.49)		
WK 70 Triglycerides (n = 10, 4)	0.3 (± 0.76)	-0.2 (± 0.25)		
LOV Triglycerides (n = 15, 4)	0.1 (± 0.64)	-0.1 (± 0.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Sitting Diastolic Blood Pressure (DPB), Sitting Systolic Blood Pressure (SBP)

End point title	Actual change from BL in Cardiovascular and other metabolic parameters: Sitting Diastolic Blood Pressure (DPB), Sitting Systolic Blood Pressure (SBP)

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: mmHG				
arithmetic mean (standard deviation)				
BL DBP (n =15, 4)	84.5 (± 7.01)	87.3 (± 4.21)		
WK 22 DPB (n = 13, 3)	0.8 (± 9.59)	2.6 (± 11.36)		
WK 70 DPB (n = 10, 4)	-3.4 (± 11.65)	-5.8 (± 12.14)		
LOV DPB (n = 15, 4)	-1.3 (± 9.23)	-3.2 (± 7.07)		
BL SBP (n =15, 4)	133.2 (± 12.51)	130.3 (± 7.75)		
WK 22 SPB (n = 13, 4)	-4.0 (± 12.46)	8.8 (± 24.74)		
WK 70 SPB (n = 10, 4)	-9.5 (± 15.78)	-4.7 (± 26.09)		
LOV SPB (n = 15, 4)	-6.2 (± 16.50)	0.3 (± 20.60)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Weight

End point title	Actual change from BL in Cardiovascular and other metabolic parameters: Weight
End point description:	
Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 22, Week 70, Last observed value	

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Kg				
arithmetic mean (standard deviation)				
BL (n =15, 4)	85.4 (± 23.52)	84.0 (± 23.32)		
WK 22 (n = 13, 4)	-2.1 (± 4.02)	0.6 (± 2.64)		
WK 70 (n = 10, 4)	-5.2 (± 4.56)	-3.2 (± 5.61)		
LOV (n = 15, 4)	-4.5 (± 6.68)	-4.4 (± 7.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Body Mass index (BMI)

End point title	Actual change from BL in Cardiovascular and other metabolic parameters: Body Mass index (BMI)

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Kg/m^2				
arithmetic mean (standard deviation)				
BL (n =15, 4)	30.6 (± 7.46)	31.3 (± 5.49)		
WK 22 (n = 13, 4)	-0.7 (± 1.42)	0.2 (± 1.09)		
WK 70 (n = 10, 4)	-1.9 (± 1.93)	-1.4 (± 2.25)		
LOV (n = 15, 4)	-1.6 (± 2.73)	-2.0 (± 2.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual change from BL in Cardiovascular and other metabolic parameters: Quantitative Insulin Sensitivity Check Index (QUICKI)

End point title	Actual change from BL in Cardiovascular and other metabolic parameters: Quantitative Insulin Sensitivity Check Index (QUICKI)

End point description:

Improving metabolic abnormalities was assessed by descriptive statistics on the change from baseline. QUICKI is the quantitative insulin sensitivity check index and is derived using the inverse of the sum of algorithms (base 10) of the fasting insulin and fasting glucose

End point type	Secondary

End point timeframe:

Baseline, Week 22, Week 70, Last observed value

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Kg/m^2				
arithmetic mean (standard deviation)				
BL (n =13, 4)	0.3 (± 0.03)	0.3 (± 0.02)		
WK 22 (n = 11, 4)	0.0 (± 0.02)	0.0 (± 0.01)		
WK 70 (n = 8, 4)	0.0 (± 0.03)	0.0 (± 0.06)		
LOV (n = 13, 4)	0.0 (± 0.04)	0.0 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: AUC0-6h ss, AUC0-12h ss

End point title	PK Parameters: AUC0-6h ss, AUC0-12h ss

End point description:

Trough PK concentrations and PK profiles at steady-state were collected.

End point type	Secondary

End point timeframe:

pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or pre-dose (trough) for maintained dose

End point values	2mg bid	5mg bid	10mg bid	20mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	13	6	1
Units: hr•ng/mL				
geometric mean (geometric coefficient of variation)				
AUC0-6h,ss	37.79 (± 42.7)	94.21 (± 37.0)	236.83 (± 29.9)	999 (± 999)
AUC0-12h,ss (n = 3,13,6,1,1)	69.96 (± 32.6)	140.65 (± 43.9)	339.62 (± 37.6)	999 (± 999)

End point values	30mg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: hr•ng/mL				
geometric mean (geometric coefficient of variation)				
AUC0-6h,ss	999 (± 999)			
AUC0-12h,ss (n = 3,13,6,1,1)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: Cmax ss, Ctrough ss

End point title	PK Parameters: Cmax ss, Ctrough ss

End point description:

Trough PK concentrations and PK profiles at steady-state were collected.

End point type	Secondary

End point timeframe:

pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or pre-dose (trough) for maintained dose

End point values	30mg bid	2mg bid	5mg bid	10mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	6	14	8
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax,ss (n =4,13,6,1,1)	999 (± 999)	8.76 (± 46.1)	23.09 (± 31.5)	59.17 (± 25.5)
Ctrough, ss	999 (± 999)	2.73 (± 49.1)	4.30 (± 112.9)	10.60 (± 104.8)

End point values	20mg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmax,ss (n =4,13,6,1,1)	999 (± 999)			
Ctrough, ss	19.69 (± 53.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: Tmax ss,

End point title	PK Parameters: Tmax ss,

End point description:

Trough PK concentrations and PK profiles at steady-state were collected.

End point type	Secondary

End point timeframe:

pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or pre-dose (trough) for maintained dose

End point values	2mg bid	5mg bid	10mg bid	20mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	13	6	1
Units: hour (hr)				
median (full range (min-max))	1.50 (1.0 to 4.1)	1.50 (1.0 to 4.0)	1.26 (1.0 to 2.0)	999 (999 to 999)

End point values	30mg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: hour (hr)				
median (full range (min-max))	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: T1/2 ss,

End point title	PK Parameters: T1/2 ss,

End point description:

Trough PK concentrations and PK profiles at steady-state were collected.

End point type	Secondary

End point timeframe:

pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or pre-dose (trough) for maintained dose

End point values	10mg bid	20mg bid	30mg bid	2mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	1	1	2
Units: hour (hr)				
geometric mean (geometric coefficient of variation)	4.32 (± 47.8)	999 (± 999)	999 (± 999)	6.39 (± 13.8)

End point values	5mg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: hour (hr)				
geometric mean (geometric coefficient of variation)	3.54 (± 49.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were responders on 24-hour urine free cortisol (UFC) at Week 22

End point title	Percentage of participants who were responders on 24-hour urine free cortisol (UFC) at Week 22

End point description:

A patient was considered to be a responder if his/her mean UFC level from the three 24-hour urine samples collected at Week 22 was ≤ ULN (as defined by the local laboratories) or represented a ≥50% decrease from baseline. Participants with controlled or partially controlled UFC were defined as: Controlled UFC: mean UFC level <= upper limit of normal (ULN). Partially controlled UFC: mean UFC level > ULN but with >= 50% reduction from baseline.

End point type	Secondary

End point timeframe:

Week 22

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Percentage pf participants				
number (confidence interval 95%)				
Responders	80.0 (51.91 to 95.67)	75.0 (19.41 to 99.37)		
Controlled UFC responders	80.0 (51.91 to 95.67)	75.0 (19.41 to 99.37)		
Partially controlled UFC responders	0 (0.00 to 21.80)	0 (0.00 to 60.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Escape

End point title	Number of participants with Escape

End point description:

Escape is defined as loss of UFC control (i.e. UFC > ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization)

End point type	Secondary

End point timeframe:

approx. 7 years

End point values	Part II Core: Expansion cohort	Part ll Core: Follow-up cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Participants	2	0		

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 end of study treatment plus 28 days post treatment, up to maximum duration of 350.6 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	Part I: Core cohort

Reporting group description:

Participants took an ascending dose of LCI699 (osilodrostat) from 2mg bid or 5 mg bid, up to 30 mg bid and participated in Part I of this study. 4 patients in this cohort moved to Part II of the study

Reporting group title	Part II Core: Expansion cohort

Reporting group description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Expansion of this study. These patients were all newly enrolled into the phase II part of the study

Reporting group title	Part II Core: Follow-up cohort

Reporting group description:

Participants took an ascending dose from 2mg bid or 5 mg bid, up to 30 mg bid and participated in the Part II Core Follow-up of this study. These patients were patients who transferred from Part I Core phase of the study.

Serious adverse events	Part I: Core cohort	Part II Core: Expansion cohort	Part II Core: Follow-up cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	5 / 15 (33.33%)	1 / 4 (25.00%)
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 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (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
Haemoglobin decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (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

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (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
Pituitary tumour benign			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (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
Vascular disorders			
Takayasu's arteritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (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
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (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
Supraventricular extrasystoles			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
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			
Headache			

subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (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 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part I: Core cohort	Part II Core: Expansion cohort	Part II Core: Follow-up cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	15 / 15 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pituitary tumour benign			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	3 / 15 (20.00%)	1 / 4 (25.00%)
occurrences (all)	0	4	1
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	5 / 15 (33.33%)	2 / 4 (50.00%)
occurrences (all)	0	5	3
Chest discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Chills			

subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	7 / 12 (58.33%)	3 / 15 (20.00%)	3 / 4 (75.00%)
occurrences (all)	9	3	3
Feeling drunk			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Generalised oedema			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Influenza like illness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	2
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	4 / 15 (26.67%)	0 / 4 (0.00%)
occurrences (all)	0	5	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)	3 / 15 (20.00%)	1 / 4 (25.00%)
occurrences (all)	1	3	1
Peripheral swelling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Breast pain			

subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dysmenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Erectile dysfunction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Menstruation delayed			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Menorrhagia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oligomenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	1 / 12 (8.33%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Dysphonia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Epistaxis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Laryngeal oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Nasal congestion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Abnormal sleep-related event			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	1 / 12 (8.33%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
Depression			
subjects affected / exposed	1 / 12 (8.33%)	2 / 15 (13.33%)	1 / 4 (25.00%)
occurrences (all)	1	2	2
Disorientation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Libido decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Sleep disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	2
Investigations			
Aldosterone urine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Amylase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood aldosterone decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood corticotrophin increased			
subjects affected / exposed	0 / 12 (0.00%)	5 / 15 (33.33%)	3 / 4 (75.00%)
occurrences (all)	0	5	3
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 12 (0.00%)	4 / 15 (26.67%)	0 / 4 (0.00%)
occurrences (all)	0	4	0
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood gonadotrophin abnormal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood luteinising hormone decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood phosphorus			

subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	2
Blood pressure decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Blood prolactin increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood testosterone free increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood testosterone increased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	4 / 4 (100.00%)
occurrences (all)	0	2	3
Blood uric acid increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Cortisol decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cortisol free urine decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Cortisol free urine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gastric pH decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Heart rate increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
High density lipoprotein decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hormone level abnormal			
subjects affected / exposed	0 / 12 (0.00%)	4 / 15 (26.67%)	3 / 4 (75.00%)
occurrences (all)	0	4	3
Lipase increased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 15 (6.67%)	2 / 4 (50.00%)
occurrences (all)	2	1	3
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Neutrophil count increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Oestradiol increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Protein total increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Renin decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urine analysis abnormal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urine leukocyte esterase			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vitamin D decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Weight increased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 15 (13.33%)	1 / 4 (25.00%)
occurrences (all)	1	2	1
White blood cell count increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Animal bite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Arthropod bite			
subjects affected / exposed	2 / 12 (16.67%)	3 / 15 (20.00%)	0 / 4 (0.00%)
occurrences (all)	2	3	0
Contusion			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Foot fracture			

subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Heat illness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Muscle injury			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Bundle branch block right			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Nervous system disorders			
Cold-stimulus headache			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	2 / 12 (16.67%)	3 / 15 (20.00%)	1 / 4 (25.00%)
occurrences (all)	2	3	2
Dizziness postural			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	3 / 12 (25.00%)	6 / 15 (40.00%)	2 / 4 (50.00%)
occurrences (all)	4	8	3
Hypersomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypogeusia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 15 (20.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Eosinophilia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Iron deficiency anaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	2	2
Polycythaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Inner ear disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Middle ear effusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Eye disorders			
Blepharospasm			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 12 (16.67%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Abdominal distension			

subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	2 / 12 (16.67%)	2 / 15 (13.33%)	3 / 4 (75.00%)
occurrences (all)	3	2	4
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	3 / 12 (25.00%)	4 / 15 (26.67%)	3 / 4 (75.00%)
occurrences (all)	3	4	7
Dry mouth			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Dysphagia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Gastric disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Haemorrhoidal haemorrhage			

subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	5 / 12 (41.67%)	8 / 15 (53.33%)	2 / 4 (50.00%)
occurrences (all)	6	10	3
Tongue disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Vomiting			
subjects affected / exposed	3 / 12 (25.00%)	1 / 15 (6.67%)	2 / 4 (50.00%)
occurrences (all)	4	1	4
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypertransaminasaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Acanthosis nigricans			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Acne			
subjects affected / exposed	1 / 12 (8.33%)	3 / 15 (20.00%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Dermal cyst			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			

subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ecchymosis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hair growth abnormal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hirsutism			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Hyperhidrosis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hypertrichosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Melanoderma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Papule			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	2 / 12 (16.67%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	5	3	1
Rash			
subjects affected / exposed	0 / 12 (0.00%)	3 / 15 (20.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Skin discolouration			

subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nephrolithiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Urinary incontinence			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 12 (0.00%)	6 / 15 (40.00%)	2 / 4 (50.00%)
occurrences (all)	0	6	3
Diabetes insipidus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Glucocorticoid deficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pituitary-dependent Cushing's syndrome			

subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 12 (16.67%)	5 / 15 (33.33%)	1 / 4 (25.00%)
occurrences (all)	2	7	1
Back pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Bone pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Bursitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Joint effusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	3 / 12 (25.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	3	1	1
Muscular weakness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Musculoskeletal stiffness			

subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Neck pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Osteopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	1	4	0
Tendonitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	6
Cystitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Furuncle			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Gastroenteritis bacterial			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Groin abscess			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Helicobacter gastritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
Laryngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	3 / 15 (20.00%)	2 / 4 (50.00%)
occurrences (all)	1	3	7
Onychomycosis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Skin infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Tongue fungal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	3 / 15 (20.00%)	3 / 4 (75.00%)
occurrences (all)	1	4	5
Viral rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Folate deficiency			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypercreatininaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hypernatraemia			

subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 15 (6.67%)	2 / 4 (50.00%)
occurrences (all)	3	1	3
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Hypoproteinaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hyposideraemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vitamin B12 deficiency			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2010	Amended the inclusion criteria to ensure that only Cushing's disease patients are enrolled; Defined responders as having a normalization of UFC or a 5 50% decrease in UFC; Revised the assumptions and power calculations to support the study sample size were revised and remove the originally planned interim analysis; Amended stopping rules to minimize premature termination of a patient from the study for AEs that were expected in this population or were efficacy related
31 January 2011	Changed the blood volume required for PD assessments.
16 March 2011	Revised and clarify the statistical analysis; Removed the need for a UFC measurement at Screening
26 March 2012	Confirmed the preliminary observations from the PoC study by: - Enrolling a new cohort (Expansion cohort) of patients. - Reenrolling the patients from the first cohort (Core PoC Follow-up cohort). - Evaluated the long-term efficacy and safety of osilodrostat treatment at 22 weeks and up to 12 months.
26 April 2013	Intensified ECG monitoring for potential risk of QTc prolongation; Excluded patients with a history of pituitary irradiation within 5 years prior to study entry; Replaced the highest dosing regimen (50 mg bid) from the dose titration schedule with a dose of 30 mg bid for those patients who did not have normalization of UFC at 20 mg bid.
14 March 2014	The purpose of this protocol amendment was to continue the study to monitor patients for long-term safety and efficacy, and to provide continued access to osilodrostat to patients who have completed long term extension-1; Provided that the investigator's assessment was that the patient would benefit from continued treatment with osilodrostat, and did not meet the protocol's termination criteria, the patient had the option to enter a second-long term extension period (extension-2), which was to continue until osilodrostat was commercially available and reimbursed or through the availability of a local access program; In addition, the protocol was updated to indicate that the formulation of osilodrostat was changed from capsules to tablets during long term extension-2.
16 February 2016	The primary purpose of this protocol amendment was to ensure patient safety by adding specific criteria for the identification and management of patients with potential drug-induced liver injury (DILI). Although there are no known cases of suspected DILI in patients treated with osilodrostat to date, these criteria are added in the event that a case of suspected DILI arises in the future; Update to the requirement for contraception by male study participants. For male subjects participating in clinical trials, contraception was no longer required; Clarification of protocol language regarding withdrawal of consent, study treatment discontinuation, and discontinuation procedures.

11 July 2017	The main purpose of this amendment was to provide continued access to the study treatment for those patients benefitting from the treatment into a separate long-term safety follow-up study (roll-over study). Based on this, the end of study (EOS) definition was updated. The EOS definition was changed throughout the protocol from "until osilodrostat is commercially available & reimbursed or through the availability of a local access program" to "patient treatment in Long Term Extension-2 will end at each site within 4 months after a separate roll-over study is opened at their site, or by 31 December 2018 (whichever occurred earlier). The roll-over study was to provide an opportunity of continued treatment for patients who were still ongoing at that time & were clinically benefitting from osilodrostat. For sites where a separate roll-over study was not an option, the patient had to be offered a local alternative treatment option. In addition, the option of an earlier End of Trial visit (i.e. earlier than the 6 month interval visits in Long Term Extension-2) was implemented to allow seamless transition of patients into the separate rollover study; The risks section was updated to include neutropenia, which is a known effect related to the decrease of cortisol in patients with Cushing's disease, in line with cases observed in clinical trials with osilodrostat. The QT-specific concomitant medication guidance for osilodrostat was revised to limit the list of prohibited drugs to medications with a 'Known risk to cause TdP" and 'Possible risk to cause TdP", instead of all drugs known to prolong QT. This change was also in alignment with the terminology used in the QT Drug Lists (CredibleMeds®); Interim Analysis was updated to allow for an additional database lock in support of future market authorization applications for osilodrostat
03 May 2018	The purpose of this amendment was to extend the study end date by a year from 31-Dec-2018 to 31-Dec-2019 to allow continued access to the study treatment for those patients benefitting from the treatment until a separate long-term safety follow-up study (roll-over study) was set up at participating sites; Additional updates were made to the Protocol glossary and withdrawal of informed consent section to align with the new Personal Data and Withdrawal of Consent language requirement.

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.novforcomplete trial results.

Notes: