Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Osilodrostat

Trial Indication(s)

All types of endogenous Cushing's syndrome except Cushing's disease

Protocol Number

CLCI699C1201

Protocol Title

A Phase II, open-label, dose titration, multi-center study to assess the safety/tolerability and efficacy of osilodrostat in patients with all types of endogenous Cushing's syndrome except Cushing's disease

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase lll

Study Start/End Dates

Study Start Date: September 2015 (Actual)
Primary Completion Date: June 2018 (Actual)
Study Completion Date: October 2018 (Actual)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a Phase II, single arm, open-label, dose titration, multi-center study which consisted of two distinct Study Periods plus an optional extension period in non-CD patients with CS. The 3 Study Periods (two distinct Study Periods plus an optional extension period) were as follows:

Study Period I [Week 0 (Day 1) to Week-12]: Study Period I was the dose titration period to achieve a stable therapeutic dose and to assess the efficacy and safety of osilodrostat.

The dosing regimen of osilodrostat in this study was to be titrated according to the following escalation sequence: osilodrostat 2 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, and 30 mg bid. Dose adjustments were based on the serum cortisol values measured by the local lab at each site. Osilodrostat titration could be done weekly for the initial 4-weeks, up to a maximum dose of 10 mg bid.

The mean of three 24-hour UFC (mUFC) values were measured to evaluate the efficacy in this period.

Study Period II (After Week-12 to Week-48): Study Period II was the period to assess the sustainability of efficacy and long term safety.
During Study Period II, only patients who tolerated and agreed to continue osilodrostat treatment continued on the study. The patient was to be administered with the stable therapeutic dose which was achieved in the Study Period I

Optional extension period (After Week-48): Patients who continue to receive clinical benefit, as assessed by the study Investigator and who wish to enter the extension period were to be reconsented at Week-48. Patients who entered the extension period were to be continued to be treated with the study drug without interruption to be assessed for efficacy and safety. Patients who continued to benefit from study treatment as assessed by the study investigator and who completed Week-72 were to be offered to participate in a separate long-term safety follow-up study. The optional extension period will end after all patients have completed Week-72 or have discontinued early.

Post-treatment Follow-up: All patients had 30 days safety follow-up after the last dose of study treatment.

Note: The data represented in the Summary of Efficacy and Summary of Safety results includes individual patient data with anonymized patient identification

Centers

Japan(4)

Objectives:

Primary objective:

- To assess the percent change from baseline in the mean Urine Free Cortisol (mUFC) at the individual patient level at Week-12.

Secondary objective:

- To assess the percent change from baseline in the mUFC at the individual patient level at Week-24 and Week-48.
- To assess the absolute and percent change from baseline in mUFC at Week-12, Week-24 and Week-48.
- To assess the complete, partial, and overall response rate at Week-12, Week-24 and Week-48.
- To assess the absolute and percent change from baseline in morning serum cortisol at the individual patient level at Week-12, Week-24 and Week-48.
- To assess the absolute and percent change from baseline in steroid hormones at the individual patient level at Week-12, Week-24 and Week-48.
- To assess the change from baseline in cardiovascular-related metabolic parameters associated with CS at Week-12, Week-24 and Week-48.
- To assess the general safety of osilodrostat.
- To assess the change from baseline in Patient-Reported Outcome (Health Related Quality of Life) at individual patient level at Week-12, Week-24 and Week-48.
- To evaluate pharmacokinetics (PK) of osilodrostat in patients with CS.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral tablets of LCI699 1 mg, 5 mg, 10 mg, 20 mg. The dosing regimen: 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.

Statistical Methods

The following analysis sets were defined:
Full analysis set (FAS) comprised of all the enrolled patients who received at least one dose of osilodrostat.

Safety analysis set included all patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment.

Pharmacokinetic analysis set (PAS) consisted of FAS who had at least one evaluable PK concentration.

There was no statistical hypothesis set up in this study. Endpoints were presented in a descriptive manner and/or summarized by frequency count and percentages for categorical data or by appropriate descriptive statistics (i.e. mean, standard deviation (SD), median, minimum and maximum) for continuous data.

Analyses of primary and all secondary efficacy endpoints were based on the FAS. Safety analyses was based on the safety analysis set. Listings were presented by disease types (ectopic corticotropin syndrome, adrenal adenoma, and AIMAH).

The change and percent change of mean Urine Free Cortisol (mUFC) were plotted over time by patient level data for the FAS. Additionally, summary was provided with corresponding 95% confidence intervals (CIs) at Weeks 12, 24 and 48.

Complete response rates (defined as the proportion of enrolled patients who have mUFC ≤ Upper normal limit (ULN)), partial response rates (defined as the proportion of enrolled patients who have mUFC>ULN and at least 50% reduction from baseline) and overall response rates (defined as the proportion of enrolled patients with mUFC ≤ ULN or at least 50% reduction from baseline) were presented along with exact 95% confidence interval at Weeks 12, 24 and 48.

The change and percent change from baseline in morning serum cortisol were summarized over time in addition to plots of individual patient data for the FAS. The changes in ACTH and other adrenal steroid hormones, and cardiovascular-related metabolic parameters associated with Cushing's syndrome were listed for the FAS.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Patients with confirmed Cushing's syndrome [i.e. ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH), or Primary Pigmented Nodular Adrenal Dysplasia (PPNAD)]
- For patients on medical treatment for hypercortisolism due to Cushing's syndrome, the washout periods had to be completed prior to baseline efficacy assessments

Exclusion Criteria:
- Patients with Cushing's disease
- History of hypersensitivity to osilodrostat or to drugs of similar chemical classes
- History of malignancy of any organ system, treated or untreated, within the past 5 years
- Patients receiving treatment for within 4 weeks or ≤5 x half-life of the agent (whichever is longer) before first dose of osilodrostat
- Patients with risk factors for QTc prolongation or Torsade de Pointes

Participant Flow Table

Overall Study

	Osilodrostat	Total
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.	
Started	9	9
Completed Week-12 (Study period I)	7	7

Discontinued at or prior to Week-12	2	2
Completed Week-12, did not enter per. II	3	3
Completed Week-12, entered Study per. II	4	4
Completed Week-48 (Study period II)	2	2
Discontinued at or prior to Week48	2	2
Compl. Wk-48, didn't enter opt. ext. per	0	0
Compl. Wk-48, entered opt. ext. period	2	2
Completed optional extension period	0	0
Discontinued study in optional ext. per.	2	2
Completed	3	3

Not Completed	6	6
Adverse Event	4	4
Subject/ Guardian decision	2	2

Baseline Characteristics

	Osilodrostat	Total
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.	
Number of Participants [units: participants]	9	9
Age Continuous (units: years) Mean ± Standard Deviation		
	51.0±18.17	
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)		
Female	7	7
Male	2	2
Race/Ethnicity, Customized (units: participants)		
Japanese	9	9

Type of disease (units: Participants)		
ACTH-Independent Macronodular Adrena;l Hyperplasia	1	1
Adrenal Adenoma	5	5
Ectopic Corticotropin Syndrome	3	3

Summary of Efficacy

Primary Outcome Result(s)

Percent change in the mean Urine Free Cortisol (mUFC) at the individual level at Week 12

(Time Frame: Baseline, 12 weeks)

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Percent change in the mean Urine Free Cortisol (mUFC) at the individual level at Week 12 (units: percentage change)	
AIMAH- Patient 1 (n=1)	-99.0
Adrenal adenoma - Patient 1 (n=1)	-97.8

Adrenal adenoma - Patient 2 (n=1)	-94.5
Adrenal adenoma - Patient 3 (n=1)	-91.5
Adrenal adenoma - Patient 4 (n=1)	-81.8
Adrenal adenoma - Patient 5 (n=1)	-52.6
Ectopic corticotropin syndrome - Patient 1 (n=1)	-99.0
Ectopic c orticotropin syndrome - Patient 2(n=0)	
Ectopic corticotropin syndrome - Patient 3 (n=0)	

Secondary Outcome Result(s)

Percent change from baseline in the mUFC at individual patient level at Week 24 (day 169) and Week 48 (day 337)

(Time Frame: Baseline, Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Percent change from baseline in the mUFC at individual patient level at Week 24 (day 169) and Week 48 (day 337)	

(units: percentage change)

AIMAH-Patient (Pt) 1: Week (Wk) 24 (n=1)	-99.5
AIMAH-Patient 1:Wk 48 (n=1)	-99.1
Adrenal adenoma-Patient 1: Wk 24(n=0)	
Adrenal adenoma-Patient 1: Wk 48(n=0)	
Adrenal adenoma-Patient 2: Wk 24(n=1)	-85.2
Adrenal adenoma-Patient 2: Wk 48(n=0)	
Adrenal adenoma-Patient 3: Wk 24(n=0)	
Adrenal adenoma-Patient 3: Wk 48(n=0)	
Adrenal adenoma-Patient 4: Wk 24(n=0)	
Adrenal adenoma-Patient 4: Wk 48(n=0)	
Adrenal adenoma-Patient 5: Wk 24(n=0)	
Adrenal adenoma-Patient 5: Wk 48(n=0)	
Ectopic corticotropin syndrome-Pt 1: Wk 24(n=1)	-91.6
Ectopic corticotropin syndrome-Pt 1: Wk 48(n=1)	-91.0

Ectopic corticotropin syndrome-Pt 2: Wk 24(n=0)
Ectopic corticotropin syndrome-Pt 2: Wk 48(n=0)
Ectopic corticotropin syndrome-Pt 3: Wk 24(n=0)
Ectopic corticotropin syndrome-Pt 3: Wk 48(n=0)

Absolute change from baseline in the mUFC at Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337)

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Absolute change from baseline in the mUFC at Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337) (units: nmol/24hr) Median (Full Range)	
Week 12 (day 85)(n = 7)	-422.10 (-10487.5 to -157.0)

Week 24 (day 169) (n = 3)	-7428.10 (-9702.0 to -367.9)
Week 48 (day 337) (n = 2)	-8521.00 (-9640.5 to -7401.5)

Percentage change from baseline in the mUFC at Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337)

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Percentage change from baseline in the mUFC at Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337) (units: percentage change) Median (Full Range)	
Week 12 (day 85)(n = 7)	-94.47 (-99.0 to -52.6)
Week 24 (day 169) (n = 3)	-91.57 (-99.5 to -85.2)
Week 48 (day 337) (n = 2)	-95.04 (-99.1 to -91.0)

Percentage of participants with mUFC response of complete, partial, and overall response

(Time Frame: 12, 24 and 48 weeks)

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	9
Percentage of participants with mUFC response of complete, partial, and overall response (units: Percentage of participants) Number (95% Confidence Interval)	
Week 12: Complete responders	66.7 (29.9 to 92.5)
Week 12: Partial responders	11.1 (0.3 to 48.2)
Week 12: Overall responders	77.8 (40.0 to 97.2)
Week 24: Complete responders (n =3)	66.7 (9.4 to 99.2)
Week 24: Partial responders (n = 3)	33.3 (0.8 to 90.6)
Week 24: Overall responders (n = 3)	100 (29.2 to 100.0)
Week 48: Complete responders (n = 2)	50.0 (1.3 to 98.7)
Week 48: Partial responders (n = 2)	50.0 (1.3 to 98.7)

Week 48: Overall responders (n = 2)	100 (15.8 to 100.0)

Absolute change from baseline in morning serum cortisol at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Absolute change from baseline in morning serum cortisol at individual level (units: nmol/L)	
AIMAH-Patient (Pt) 1: Week (Wk) 12 (n = 1)	-607
AIMAH-Patient 1: Wk 24 (n = 1)	-571
AIMAH-Patient 1: Wk 48 (n = 1)	-580
Adrenal adenoma-Patient 1: Wk 12 (n =1)	-334
Adrenal adenoma-Patient 1:Wk 24 (n =0)	
Adrenal adenoma-Patient 1: Wk 48 (n =0)	

Adrenal adenoma-Patient 2: Wk 12(n =1)	-157
Adrenal adenoma-Patient 2: Wk 24 (n =1)	-135
Adrenal adenoma-Patient 2: Wk 48 (n =0)	
Adrenal adenoma-Patient 3: Wk 12 (n =1)	-300
Adrenal adenoma-Patient 3: Wk 24 (n =0)	
Adrenal adenoma-Patient 3: Wk 48 (n =0)	
Adrenal adenoma-Patient 4: Wk 12 (n =1)	-30
Adrenal adenoma-Patient 4: Wk 24 (n =0)	
Adrenal adenoma-Patient 4: Wk 48 (n =0)	
Adrenal adenoma-Patient 5: Wk 12 (n =1)	-13
Adrenal adenoma-Patient 5: Wk 24 (n =0)	
Adrenal adenoma-Patient 5: Wk 48 (n =0)	
Ectopic corticotropin syndrome-Pt 1: Wk 12 (n =1)	-949
Ectopic corticotropin syndrome-Pt 1: Wk24 (n=1)	-927
Ectopic corticotropin syndrome-Pt 1: Wk48 (n=1)	-861

Ectopic corticotropin syndrome-Pt 2: Wk 12 (n =0)
Ectopic corticotropin syndrome-Pt 2: Wk 24 (n=0)
Ectopic corticotropin syndrome-Pt 2: Wk48 (n=0)
Ectopic corticotropin syndrome-Pt 3: Wk 12 (n =0)
Ectopic corticotropin syndrome-Pt 3: Wk24 (n=0)
Ectopic corticotropin syndrome-Pt 3: Wk48 (n=0)

Percentage change from baseline in morning serum cortisol at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Percentage change from baseline in morning serum cortisol at individual level	

(units: percentage change)

AIMAH-Patient (Pt) 1: Week (Wk) 12 (n = 1)	-73.3
AIMAH-Patient 1: Wk 24 (n = 1)	-69.0
AIMAH-Patient 1: Wk 48 (n = 1)	-70.0
Adrenal adenoma-Patient 1: Wk 12 (n =1)	-78.0
Adrenal adenoma-Patient 1:Wk 24 (n =0)	
Adrenal adenoma-Patient 1: Wk 48 (n =0)	
Adrenal adenoma-Patient 2: Wk 12(n =1)	-50.8
Adrenal adenoma-Patient 2: Wk 24 (n =1)	-43.7
Adrenal adenoma-Patient 2: Wk 48 (n =0)	
Adrenal adenoma-Patient 3: Wk 12 (n =1)	-56.1
Adrenal adenoma-Patient 3: Wk 24 (n =0)	
Adrenal adenoma-Patient 3: Wk 48 (n =0)	
Adrenal adenoma-Patient 4: Wk 12 (n =1)	-8.7
Adrenal adenoma-Patient 4: Wk 24 (n =0)	
Adrenal adenoma-Patient 4: Wk 48 (n =0)	

Adrenal adenoma-Patient 5: Wk 12 (n =1)	-3.5
Adrenal adenoma-Patient 5: Wk 24 (n =0)	
Adrenal adenoma-Patient 5: Wk 48 (n =0)	
Ectopic corticotropin syndrome-Pt 1: Wk 12 (n =1)	-71.4
Ectopic corticotropin syndrome-Pt 1: Wk24 (n=1)	-69.7
Ectopic corticotropin syndrome-Pt 1: Wk48 (n=1)	-64.7
Ectopic corticotropin syndrome-Pt 2: Wk 12 (n =0)	
Ectopic corticotropin syndrome-Pt 2: Wk24 (n=0)	
Ectopic corticotropin syndrome-Pt 2: Wk48 (n=0)	
Ectopic corticotropin syndrome-Pt 3: Wk 12 (n =0)	
Ectopic corticotropin syndrome-Pt 3: Wk24 (n=0)	
Ectopic corticotropin syndrome-Pt 3: Wk48 (n=0)	

Absolute change from baseline in ACTH and other adrenal steroid hormones at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	ACTH	Serum 11-deoxycorticosterone	Aldosterone	Estradiol
Arm/Group Description	Adrenocorticotropic hormone	adrenal steroid hormones: Serum 11-deoxycorticosterone	adrenal steroid hormones: Aldosterone	adrenal steroid hormones: Estradiol
Number of Participants Analyzed [units: participants]	7	7	7	7
Absolute change from baseline in ACTH and other adrenal steroid hormones at individual level (units: pmol/L)				
AIMAH-Patient (Pt) 1 Wk 12 (n=1,1,1,1)	0	2179	52	705
AIMAH-Pt 1 Wk 24 (n=1,1,1,1)	0	3601	236	235
AIMAH-Pt 1 Wk 48 (n=1,1,1,1)	0	454	170	400
Adrenal adenoma-Pt 1 Wk 12 (n=1,1,1,1)	1.1	2966	-27	-404
Adrenal adenoma-Pt 1 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 1 Wk 48 (n=0,0,0,0)				
Adrenal adenoma-Pt 2 Wk 12 (n=1,1,1,1)	0	5145	-981	4
Adrenal adenoma-Pt 2 Wk 24(n=1,1,1,1)	0	0	450	-4
Adrenal adenoma-Pt 2 Wk 48 (n=0,0,0,0)				

Adrenal adenoma-Pt 3 Wk 12 (n=1,1,1,1)	0	0	-147	77
Adrenal adenoma-Pt 3 Wk 24 (n=0, 0,0,0)				
Adrenal adenoma-Pt 3 Wk 48(n=0,0,0,0)				
Adrenal adenoma-Pt 4 Wk 12 (n=1,1,1,1)	0	787	3	18
Adrenal adenoma-Pt 4 Wk 24 (n=0,0,0,0)				
Adrenal adenoma-Pt 4 Wk 48 (n=0,0,0,0)				
Adrenal adenoma-Pt 5 Wk 12 (n=1,1,1,1)	0	0	0	-11
Adrenal adenoma-Pt 5 Wk 24 (n=0,0,0,0)				
Adrenal adenoma-Pt 5 Wk 48 (n=0,0,0,0)				
Ectopic ACTH syndrome-Pt 1: Wk 12 (n=1,1,1,1)	-67.7	-696	145	51
Ectopic ACTH syndrome-Pt 1: Wk 24 (n=1,1,1,1)	-47.3	-91	40	-11
Ectopic ACTH syndrome-Pt 1: Wk 48 (n=1,1,1,1)	13.3	-91	37	11
Ectopic ACTH syndrome-Pt 2: Wk 12 (n=0,0,0,0)				
Ectopic ACTH syndrome-Pt 2: Wk 24 (n=0,0,0,0)				
Ectopic ACTH syndrome-Pt 2: Wk 48 (n=0,0,0,0)				
Ectopic ACTH syndrome-Pt 3: Wk 12 (n=0,0,0,0)				

Ectopic ACTH syndrome-Pt 3: Wk 24 (n=0,0,0,0)
Ectopic ACTH syndrome-Pt 3: Wk 48 (n=0,0,0,0)

Percentage change from baseline in ACTH and other adrenal steroid hormones at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	ACTH	Serum 11-deoxycorticosterone	Aldosterone	Estradiol
Arm/Group Description	Adrenocorticotropic hormone	adrenal steroid hormones: Serum 11-deoxycorticosterone	adrenal steroid hormones: Aldosterone	adrenal steroid hormones: Estradiol
Number of Participants Analyzed [units: participants]	7	7	7	7
Percentage change from baseline in ACTH and other adrenal steroid hormones at individual level (units: percentage change)				
AIMAH-Patient (Pt) 1 Wk 12 (n =0,1,0,1)		118.0		1282
AIMAH-Pt 1 Wk 24 (n=0,1,0,1)		195.1		427.3
AIMAH-Pt 1 Wk 48 (n=0,1,0,1)		24.6		727.3
Adrenal adenoma-Pt 1 Wk 12 (n =0,0,1,1)			-13.9	-53.7
Adrenal adenoma-Pt 1 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 1 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 2 Wk 12 (n =0,0,1,1)			-100	1.9

Adrenal adenoma-Pt 2 Wk 24 (n =0,0,1,1)			45.9	-1.9
Adrenal adenoma-Pt 2 Wk 48 (n =0,0,0, 0)				
Adrenal adenoma-Pt 3 Wk 12 (n =0,0,1,1)			-75.0	513.3
Adrenal adenoma-Pt 3 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 3 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 4 Wk 12 (n =0,0,1,1)			10.0	120.0
Adrenal adenoma-Pt 4 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 4 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 5 Wk 12 (n =0,0,0,1)				-100
Adrenal adenoma-Pt 5 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 5 Wk 48 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 1: Wk 12 (n=1,1,0,1)	-71.6	-100		72.9
Ectopic ACTH syndrome-Pt 1: Wk 24 (n=1,1,0,1)	-50.0	-13.1		-15.7
Ectopic ACTH syndrome-Pt 1: Wk 48 (n=1,1,0,1)	14.1	-13.1		15.7
Ectopic ACTH syndrome-Pt 2: Wk 12 (n=0,0,0,0)				
Ectopic ACTH syndrome-Pt 2 Wk 24 (n =0,0,0,0)				

Ectopic ACTH syndrome-Pt 2 Wk 48 (n =0,0,0,0)
Ectopic ACTH syndrome-Pt 3 Wk 12 (n =0,0,0,0)
Ectopic ACTH syndrome-Pt 3 Wk 24 (n =0,0,0,0)
Ectopic ACTH syndrome-Pt 3 Wk 48 (n =0,0,0,0)

Absolute change from baseline in other adrenal steroid hormones at individual levels

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Serum 11-deoxycortisol	Testosterone
Arm/Group Description	adrenal steroid hormones: Serum 11-deoxycortisol	adrenal steroid hormones: Testosterone
Number of Participants Analyzed [units: participants]	7	7
Absolute change from baseline in other adrenal steroid hormones at individual levels (units: nmol/L)		
AIMAH-Patient (Pt) 1 Wk 12 (n = 1,1)	-4.35	0.76
AIMAH-Pt 1 Wk 24 (n = 1,1)	-8.5	0.66
AIMAH-Pt 1 Wk 48 (n = 1,1)	-15.54	-0.03
Adrenal adenoma-Pt 1 Wk 12 (n = 1,1)	6.91	0.31

Adrenal adenoma-Pt 1 Wk 24 (n =0,0)		
Adrenal adenoma-Pt 1 Wk 48 (n =0,0)		
Adrenal adenoma-Pt 2 Wk 12 (n = 1,1)	2.81	0.11
Adrenal adenoma-Pt 2 Wk 24 (n = 1,1)	-0.64	-0.35
Adrenal adenoma-Pt 2 Wk 48 (n = 0,0)		
Adrenal adenoma-Pt 3 Wk 12 (n = 1,1)	7.34	0.42
Adrenal adenoma-Pt 3 Wk 24 (n = 0, 0)		
Adrenal adenoma-Pt 3 Wk 48 (n =0,0)		
Adrenal adenoma-Pt 4 Wk 12 (n = 1,1)	3.5	0.03
Adrenal adenoma-Pt 4 Wk 24 (n = 0,0)		
Adrenal adenoma-Pt 4 Wk 48 (n = 0,0)		
Adrenal adenoma-Pt 5 Wk 12 (n = 1,1)	-1.39	0
Adrenal adenoma-Pt 5 Wk 24 (n =0,0)		
Adrenal adenoma-Pt 5 Wk 48 (n = 0,0)		
Ectopic ACTH syndrome-Pt 1 Wk 12(n = 1,1)	-15.81	5.83
Ectopic ACTH syndrome-Pt 1 Wk 24 (n = 1,1)	-12.41	-2.71

Ectopic ACTH syndrome-Pt 1 Wk 48 (n = 1,1)	-2.52	-2.01
Ectopic ACTH syndrome-Pt 2 Wk 12 (n = 0,0)		
Ectopic ACTH syndrome-Pt 2 Wk 24 (n = 0,0)		
Ectopic ACTH syndrome-Pt 2 Wk 48 (n = 0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 12(n =0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 24 (n = 0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 48(n = 0,0)		

Percentage change from baseline in other adrenal steroid hormones at individual levels

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Serum 11-deoxycortisol	Testosterone
Arm/Group Description	adrenal steroid hormones: Serum 11-deoxycortisol	adrenal steroid hormones: Testosterone
Number of Participants Analyzed [units: participants]	7	7
Percentage change from baseline in other adrenal steroid hormones at individual levels (units: percentage change)		
AIMAH-Patient (Pt) 1 Wk 12 (n=1, 1)	-17.8	73.1

AIMAH-Pt 1 Wk 24 (n=1, 1)	-34.9	63.5
AIMAH-Pt 1 Wk 48 (n=1, 1)	-63.7	-2.9
Adrenal adenoma-Pt 1 Wk 12 (n=1,1)	143.7	100.0
Adrenal adenoma-Pt 1 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 1 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 2 Wk 12 (n=1,1)	108.9	10.6
Adrenal adenoma-Pt 2 Wk 24 (n=1,1)	-24.8	-33.7
Adrenal adenoma-Pt 2 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 3 Wk 12 (n=1, 1)	127.2	93.3
Adrenal adenoma-Pt 3 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 3 Wk 48 (n=0,0		
Adrenal adenoma-Pt 4 Wk 12 (n=1, 1)	267.2	14.3
Adrenal adenoma-Pt 4 Wk 24 (n=0,0		
Adrenal adenoma-Pt 4 Wk 48 (n=0,0		
Adrenal adenoma-Pt 5 Wk 12 (n=1,1)	-43.2	0.0
Adrenal adenoma-Pt 5 Wk 24 (n=0,0)		

Adrenal adenoma-Pt 5 Wk 48 (n=0,0)		
Ectopic ACTH syndrome-Pt 1 Wk 12 (n=1, 1)	-64.8	96.5
Ectopic ACTH syndrome-Pt 1 Wk 24 (n=1, 1)	-50.9	-44.9
Ectopic ACTH syndrome-Pt 1 Wk 48 (n=1, 1)	-10.3	-33.3
Ectopic ACTH syndrome-Pt 2 Wk 12 (n=0,0)		
Ectopic ACTH syndrome-Pt 2 Wk 24 (n=0,0)		
Ectopic ACTH syndrome-Pt 2 Wk 48 (n=0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 12(n=0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 24 (n=0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 48 (n=0,0)		

Absolute change from baseline in cardiovascular-related metabolic parameter, fasting glucose, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7

Absolute change from baseline in cardiovascular-related metabolic parameter, fasting glucose, at individual level
(units: mmol/L)

AIMAH-Patient (Pt) 1 Wk 12 (n =1)	-0.78
AIMAH-Patient (Pt) 1 Wk 24 (n =1)	-0.84
AIMAH-Patient (Pt) 1 Wk 48 (n =1)	-0.78
Adrenal adenoma-Pt 1 Wk 12 (n =1)	1.22
Adrenal adenoma-Pt 1 Wk 24 (n =0)	
Adrenal adenoma-Pt 1 Wk 48 (n =0)	
Adrenal adenoma-Pt 2 Wk 12 (n =1)	-1.89
Adrenal adenoma-Pt 2 Wk 24 (n =1)	0.22
Adrenal adenoma-Pt 2 Wk 48 (n =0)	
Adrenal adenoma-Pt 3 Wk 12 (n =1)	-0.28
Adrenal adenoma-Pt 3 Wk 24 (n =0)	
Adrenal adenoma-Pt 3 Wk 48 (n =0)	
Adrenal adenoma-Pt 4 Wk 12 (n =1)	-0.67

Adrenal adenoma-Pt 4 Wk 24 (n =0)	
Adrenal adenoma-Pt 4 Wk 48 (n =0)	
Adrenal adenoma-Pt 5 Wk 12 (n =1)	-0.05
Adrenal adenoma-Pt 5 Wk 24 (n =0)	
Adrenal adenoma-Pt 5 Wk 48 (n =0)	
Ectopic ACTH syndrome-Pt 1 Wk 12 (n =1)	-0.33
Ectopic ACTH syndrome-Pt 1 Wk 24 (n =1)	-0.39
Ectopic ACTH syndrome-Pt 1 Wk 48 (n =1)	0.06
Ectopic ACTH syndrome-Pt 2 Wk 12 (n=0)	
Ectopic ACTH syndrome-Pt 2 Wk 24 (n =0)	
Ectopic ACTH syndrome-Pt 2 Wk 48 (n =0)	
Ectopic ACTH syndrome-Pt 3 Wk 12 (n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 24 (n =0)	
Ectopic ACTH syndrome-Pt 3 Wk 48 (n =0)	

Percentage change from baseline in cardiovascular-related metabolic parameter, fasting glucose, at individual level
(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Percentage change from baseline in cardiovascular-related metabolic parameter, fasting glucose, at individual level (units: percentage change)	
AIMAH-Patient (Pt) 1 Wk 12 (n =1)	-15.3
AIMAH-Patient (Pt) 1 Wk 24 (n =1)	-16.4
AIMAH-Patient (Pt) 1 Wk 48 (n =1)	-15.3
Adrenal adenoma-Pt 1 Wk 12 (n =1)	24.2
Adrenal adenoma-Pt 1 Wk 24 (n =0)	
Adrenal adenoma-Pt 1 Wk 48 (n =0)	
Adrenal adenoma-Pt 2 Wk 12 (n =1)	-27.2
Adrenal adenoma-Pt 2 Wk 24 (n =1)	3.2
Adrenal adenoma-Pt 2 Wk 48 (n =0)	

Adrenal adenoma-Pt 3 Wk 12 (n =1)	-5.0
Adrenal adenoma-Pt 3 Wk 24 (n =0)	
Adrenal adenoma-Pt 3 Wk 48 (n =0)	
Adrenal adenoma-Pt 4 Wk 12 (n =1)	-11.3
Adrenal adenoma-Pt 4 Wk 24 (n =0)	
Adrenal adenoma-Pt 4 Wk 48 (n =0)	
Adrenal adenoma-Pt 5 Wk 12 (n =1)	-0.9
Adrenal adenoma-Pt 5 Wk 24 (n =0)	
Adrenal adenoma-Pt 5 Wk 48 (n =0)	
Ectopic ACTH syndrome-Pt 1 Wk 12 (n =1)	-5.9
Ectopic ACTH syndrome-Pt 1 Wk 24 (n =1)	-7.0
Ectopic ACTH syndrome-Pt 1 Wk 48 (n =1)	1.1
Ectopic ACTH syndrome-Pt 2 Wk 12 (n=0)	
Ectopic ACTH syndrome-Pt 2 Wk 24 (n =0)	
Ectopic ACTH syndrome-Pt 2 Wk 48 (n =0)	
Ectopic ACTH syndrome-Pt 3 Wk 12 (n=0)	

Ectopic ACTH syndrome-Pt 3 Wk 24 (n =0)
Ectopic ACTH syndrome-Pt 3 Wk 48 (n =0)

Absolute change from baseline in cardiovascular-related metabolic parameter, HbA1c, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Absolute change from baseline in cardiovascular-related metabolic parameter, HbA1c, at individual level (units: percentage of HbA1c)	
AIMAH-Patient (Pt) 1 Wk 12 (n=1)	-0.1
AIMAH-Pt 1 Wk 24 (n=1)	-0.1
AIMAH-Pt 1 Wk 48 (n=1)	-0.2
Adrenal adenoma-Pt 1 Wk 12 (n=1)	0.3
Adrenal adenoma-Pt 1 Wk 24 (n=0)	
Adrenal adenoma-Pt 1 Wk 48 (n=0)	

Adrenal adenoma-Pt 2 Wk 12 (n=1)	-0.4
Adrenal adenoma-Pt 2 Wk 24 (n=1)	-0.7
Adrenal adenoma-Pt 2 Wk 48 (n=0)	
Adrenal adenoma-Pt 3 Wk 12 (n=1)	-1.4
Adrenal adenoma-Pt 3 Wk 24 (n=0)	
Adrenal adenoma-Pt 3 Wk 48 (n=0)	
Adrenal adenoma-Pt 4 Wk 12 (n=1)	-0.9
Adrenal adenoma-Pt 4 Wk 24 (n=0)	
Adrenal adenoma-Pt 4 Wk 48 (n=0)	
Adrenal adenoma-Pt 5 Wk 12 (n=1)	-0.1
Adrenal adenoma-Pt 5 Wk 24 (n=0)	
Adrenal adenoma-Pt 5 Wk 48 (n=0)	
Ectopic ACTH syndrome-Pt 1 Wk 12 (n=1)	0.3
Ectopic ACTH syndrome-Pt 1 Wk 24 (n=1)	0.5
Ectopic ACTH syndrome-Pt 1 Wk 48 (n=1)	0.8
Ectopic ACTH syndrome-Pt 2 Wk 12(n=0)	

Ectopic ACTH syndrome-Pt 2 Wk 24 (n=0)
Ectopic ACTH syndrome-Pt 2 Wk 48 (n=0)
Ectopic ACTH syndrome-Pt 3 Wk 12(n=0)
Ectopic ACTH syndrome-Pt 3 Wk 24 (n=0)
Ectopic ACTH syndrome-Pt 3 Wk 48 (n=0)

Percentage change from baseline in cardiovascular-related metabolic parameter, HbA1c, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Percentage change from baseline in cardiovascular-related metabolic parameter, HbA1c, at individual level (units: percentage change)	
AIMAH-Patient (Pt) 1 Wk 12 (n=1)	-1.8
AIMAH-Pt 1 Wk 24 (n=1)	-1.8
AIMAH-Pt 1 Wk 48 (n=1)	-3.6

Adrenal adenoma-Pt 1 Wk 12 (n=1)	6.2
Adrenal adenoma-Pt 1 Wk 24 (n=0)	
Adrenal adenoma-Pt 1 Wk 48 (n=0)	
Adrenal adenoma-Pt 2 Wk 12 (n=1)	-6.5
Adrenal adenoma-Pt 2 Wk 24 (n=1)	-11.3
Adrenal adenoma-Pt 2 Wk 48 (n=0)	
Adrenal adenoma-Pt 3 Wk 12 (n=1)	-20.3
Adrenal adenoma-Pt 3 Wk 24 (n=0)	
Adrenal adenoma-Pt 3 Wk 48 (n=0)	
Adrenal adenoma-Pt 4 Wk 12 (n=1)	-12.2
Adrenal adenoma-Pt 4 Wk 24 (n=0)	
Adrenal adenoma-Pt 4 Wk 48 (n=0)	
Adrenal adenoma-Pt 5 Wk 12 (n=1)	-1.5
Adrenal adenoma-Pt 5 Wk 24 (n=0)	
Adrenal adenoma-Pt 5 Wk 48 (n=0)	
Ectopic ACTH syndrome-Pt 1 Wk 12 (n=1)	5.4

Ectopic ACTH syndrome-Pt 1 Wk 24 (n=1)	8.9
Ectopic ACTH syndrome-Pt 1 Wk 48 (n=1)	14.3
Ectopic ACTH syndrome-Pt 2 Wk 12(n=0)	
Ectopic ACTH syndrome-Pt 2 Wk 24 (n=0)	
Ectopic ACTH syndrome-Pt 2 Wk 48 (n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 12(n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 24 (n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 48 (n=0)	

Absolute change from baseline in cardiovascular-related metabolic parameters, Cholesterol, HDL cholesterol, LDL cholesterol & Triglycerides, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.	Patients in this arm took the study drug, osilodrostat.	Patients in this arm took the study drug, osilodrostat.	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7	7	7	7

Absolute change from baseline in cardiovascular-related metabolic parameters, Cholesterol, HDL cholesterol, LDL cholesterol & Triglycerides, at individual level

(units: mmol/L)

AIMAH-Patient (Pt) 1 Wk 12 (n =1,1,1,1)	-0.67	-0.85	0.21	-0.87
AIMAH-Pt 1 Wk 24 (n =1,1,1,1)	-0.65	-1.01	0.18	-0.64
AIMAH-Pt 1 Wk 48 (n =1,1,1,1)	-0.72	-0.57	-0.08	-0.76
Adrenal adenoma-Pt 1 Wk 12 (n =1,1,1,1)	-1.56	-0.26	-1.11	-1.42
Adrenal adenoma-Pt 1 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 1 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 2 Wk 12 (n =1,1,1,1)	-0.54	-0.64	-0.26	0.11
Adrenal adenoma-Pt 2 Wk 24 (n =1,1,1,1)	0.26	-0.33	0.31	0.08
Adrenal adenoma-Pt 2 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 3 Wk 12 (n =1,1,1,1)	-0.55	-0.16	-0.19	-1.36
Adrenal adenoma-Pt 3 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 3 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 4 Wk 12 (n =1,1,1,1)	1.09	0.18	0.72	0.58
Adrenal adenoma-Pt 4 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt Wk 48 (n =0,0,0,0)				

Adrenal adenoma-Pt 5 Wk 12 (n =1,1,1,1)	-0.39	-0.21	-0.18	0.44
Adrenal adenoma-Pt 5 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 5 Wk 48 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 1 Wk 12(n =1,1,1,1)	-0.16	0.16	-0.11	-0.47
Ectopic ACTH syndrome-Pt 1 Wk 24 (n =1,1,1,1)	-0.26	0.49	-0.29	-0.83
Ectopic ACTH syndrome-Pt 1 Wk 48 (n =1,1,1,1)	-0.08	0.29	-0.31	0.22
Ectopic ACTH syndrome-Pt 2 Wk 12 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 2 Wk 24 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 2 Wk 48 (n =0,0,0,0,)				
Ectopic ACTH syndrome-Pt 3 Wk 12 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 3 Wk 24 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 3 Wk 48 (n =0,0,0,0)				

Percentage change from baseline in cardiovascular-related metabolic parameters, Cholesterol, HDL cholesterol, LDL cholesterol & Triglycerides, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides
Arm/Group Description	Patients in this arm took the study	Patients in this arm took the study	Patients in this arm took the study	Patients in this arm took the study

	drug, osilodrostat.	drug, osilodrostat.	drug, osilodrostat.	drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7	7	7	7
Percentage change from baseline in cardiovascular-related metabolic parameters, Cholesterol, HDL cholesterol, LDL cholesterol & Triglycerides, at individual level (units: percentage change)				
AIMAH-Patient (Pt) 1 Wk 12 (n =1,1,1,1)	-11.1	-33.2	6.3	-49.4
AIMAH-Pt 1 Wk 24 (n =1,1,1,1)	-10.7	-39.5	5.4	-36.4
AIMAH-Pt 1 Wk 48 (n =1,1,1,1)	-11.9	-22.3	-2.4	-43.2
Adrenal adenoma-Pt 1 Wk 12 (n =1,1,1,1)	-23.0	-27.1	-24.9	-28.8
Adrenal adenoma-Pt 1 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 1 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 2 Wk 12 (n =1,1,1,1)	-11.9	-34.4	-10.6	12.5
Adrenal adenoma-Pt 2 Wk 24 (n =1,1,1,1)	5.7	-17.7	12.6	9.1
Adrenal adenoma-Pt 2 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 3 Wk 12 (n =1,1,1,1)	-9.5	-9.4	-5.5	-56.7
Adrenal adenoma-Pt 3 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 3 Wk 48 (n =0,0,0,0)				

Adrenal adenoma-Pt 4 Wk 12 (n =1,1,1,1)	23.0	15.5	26.5	46.8
Adrenal adenoma-Pt 4 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 4 Wk 48 (n =0,0,0,0)				
Adrenal adenoma-Pt 5 Wk 12 (n =1,1,1,1)	-8.7	-11.4	-9.3	33.3
Adrenal adenoma-Pt 5 Wk 24 (n =0,0,0,0)				
Adrenal adenoma-Pt 5 Wk 48 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 1 Wk 12(n =1,1,1,1)	-3.8	12.4	-4.5	-32.0
Ectopic ACTH syndrome-Pt 1 Wk 24 (n =1,1,1,1)	-6.2	38.0	-11.8	-56.5
Ectopic ACTH syndrome-Pt 1 Wk 48 (n =1,1,1,1)	-1.9	22.5	-12.6	15.0
Ectopic ACTH syndrome-Pt 2 Wk 12 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 2 Wk 24 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 2 Wk 48 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 3 Wk 12 (n =0,0,0,0)				
Ectopic ACTH syndrome-Pt 3 Wk 48 (n =0,0,0,0)				

Absolute change from baseline in cardiovascular-related metabolic parameter, BMI, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Absolute change from baseline in cardiovascular-related metabolic parameter, BMI, at individual level (units: kg/m^2)	
AIMAH-Patient (Pt) 1 Wk 12 (n =1)	-0.5
AIMAH-Pt 1 Wk 24 (n =1)	-2.3
AIMAH-Pt 1 Wk 48 (n =1)	-1.6
Adrenal adenoma-Pt 1 Wk 12 (n =1)	0.6
Adrenal adenoma-Pt 1 Wk 24 (n =0)	
Adrenal adenoma-Pt 1 Wk 48 (n =0)	
Adrenal adenoma-Pt 2 Wk 12 (n =1)	-1.2
Adrenal adenoma-Pt 2 Wk 24 (n =1)	-3.6
Adrenal adenoma-Pt 2 Wk 48 (n =0)	
Adrenal adenoma-Pt 3 Wk 12 (n =1)	0.7

Adrenal adenoma-Pt 3 Wk 24 (n =0)	
Adrenal adenoma-Pt 3 Wk 48 (n =0)	
Adrenal adenoma-Pt 4 Wk 12 (n =1)	0.2
Adrenal adenoma-Pt 4 Wk 24 (n =0)	
Adrenal adenoma-Pt 4 Wk 48 (n =0)	
Adrenal adenoma-Pt 5 Wk 12 (n =1)	0.1
Adrenal adenoma-Pt 5 Wk 24 (n =0)	
Adrenal adenoma-Pt 5 Wk 48 (n =0)	
Ectopic ACTH syndrome-Pt 1 Wk 12(n =1)	1.8
Ectopic ACTH syndrome-Pt 1 Wk 24 (n =1)	3.0
Ectopic ACTH syndrome-Pt 1 Wk 48 (n =1)	3.6
Ectopic ACTH syndrome-Pt 2 Wk 12(n =0)	
Ectopic ACTH syndrome-Pt 2 Wk 24 (n =0)	
Ectopic ACTH syndrome-Pt 2 Wk 48 (n =0)	
Ectopic ACTH syndrome-Pt 3 Wk 12 (n =0)	
Ectopic ACTH syndrome-Pt 3 Wk 24 (n =0)	

Ectopic ACTH syndrome-
Pt 3 Wk 48 (n =0)

Percentage change from baseline in cardiovascular-related metabolic parameter, BMI, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Percentage change from baseline in cardiovascular-related metabolic parameter, BMI, at individual level (units: percentage change)	
AIMAH-Patient (Pt) 1 Wk 12 (n =1)	-2.1
AIMAH-Pt 1 Wk 24 (n =1)	-9.6
AIMAH-Pt 1 Wk 48 (n =1)	-6.7
Adrenal adenoma-Pt 1 Wk 12 (n =1)	1.9
Adrenal adenoma-Pt 1 Wk 24 (n =0)	
Adrenal adenoma-Pt 1 Wk 48 (n =0)	
Adrenal adenoma-Pt 2 Wk 12 (n =1)	-3.1

Adrenal adenoma-Pt 2 Wk 24 (n =1)	-9.4
Adrenal adenoma-Pt 2 Wk 48 (n =0)	
Adrenal adenoma-Pt 3 Wk 12 (n =1)	3.3
Adrenal adenoma-Pt 3 Wk 24 (n =0)	
Adrenal adenoma-Pt 3 Wk 48 (n =0)	
Adrenal adenoma-Pt 4 Wk 12 (n =1)	0.9
Adrenal adenoma-Pt 4 Wk 24 (n =0)	
Adrenal adenoma-Pt 4 Wk 48 (n =0)	
Adrenal adenoma-Pt 5 Wk 12 (n =1)	0.5
Adrenal adenoma-Pt 5 Wk 24 (n =0)	
Adrenal adenoma-Pt 5 Wk 48 (n =0)	
Ectopic ACTH syndrome-Pt 1 Wk 12(n =1)	7.4
Ectopic ACTH syndrome-Pt 1 Wk 24 (n =1)	12.3
Ectopic ACTH syndrome-Pt 1 Wk 48 (n =1)	14.8
Ectopic ACTH syndrome-Pt 2 Wk 12(n =0)	
Ectopic ACTH syndrome-Pt 2 Wk 24 (n =0)	

Ectopic ACTH syndrome-Pt 2 Wk 48 (n =0)	
Ectopic ACTH syndrome-Pt 3 Wk 12 (n =0)	
Ectopic ACTH syndrome-Pt 3 Wk 24 (n =0)	
Ectopic ACTH syndrome-Pt 3 Wk 48 (n =0)	

Absolute change from baseline in cardiovascular-related metabolic parameter, Waist circumference, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Absolute change from baseline in cardiovascular-related metabolic parameter, Waist circumference, at individual level (units: cm)	
AIMAH-Patient (Pt)1 Wk 12 (n=1)	-2.0
AIMAH-Pt1 Wk 24 (n=1)	-7.5
AIMAH-Pt1 Wk 48 (n=1)	-5.5
Adrenal adenoma-Pt 1 Wk 12 (n=1)	-2.0

Adrenal adenoma-Pt 1 Wk 24 (n=0)	
Adrenal adenoma-Pt 1 Wk 48 (n=0)	
Adrenal adenoma-Pt 2 Wk 12 (n=1)	-1.0
Adrenal adenoma-Pt 2 Wk 24 (n=1)	-8.0
Adrenal adenoma-Pt 2 Wk 48 (n=0)	
Adrenal adenoma-Pt 3 Wk 12 (n=1)	-4.0
Adrenal adenoma-Pt 3 Wk 24 (n=0)	
Adrenal adenoma-Pt 3 Wk 48 (n=0)	
Adrenal adenoma-Pt 4 Wk 12 (n=1)	1.0
Adrenal adenoma-Pt 4 Wk 24 (n=0)	
Adrenal adenoma-Pt 4 Wk 48 (n=0)	
Adrenal adenoma-Pt 5 Wk 12 (n=1)	-0.3
Adrenal adenoma-Pt 5 Wk 24 (n=0)	
Adrenal adenoma-Pt 5 Wk 48 (n=0)	
Ectopic ACTH syndrome-Pt 1 Wk 12 (n=1)	2.5
Ectopic ACTH syndrome-Pt 1 Wk 24 (n=1)	11.0

Ectopic ACTH syndrome-Pt 1 Wk 48 (n=1)	9.5
Ectopic ACTH syndrome-Pt 2 Wk 12 (n=0)	
Ectopic ACTH syndrome-Pt 2 Wk 24 (n=0)	
Ectopic ACTH syndrome-Pt 2 Wk 48 (n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 12(n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 24 (n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 48 (n=0)	

Percentage change from baseline in cardiovascular-related metabolic parameter, Waist circumference, at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Percentage change from baseline in cardiovascular-related metabolic parameter, Waist circumference, at individual level (units: percentage change)	

AIMAH-Patient (Pt)1 Wk 12 (n=1)	-2.4
AIMAH-Pt1 Wk 24 (n=1)	-9.0
AIMAH-Pt1 Wk 48 (n=1)	-6.6
Adrenal adenoma-Pt 1 Wk 12 (n=1)	-1.8
Adrenal adenoma-Pt 1 Wk 24 (n=0)	
Adrenal adenoma-Pt 1 Wk 48 (n=0)	
Adrenal adenoma-Pt 2 Wk 12 (n=1)	-0.9
Adrenal adenoma-Pt 2 Wk 24 (n=1)	-7.1
Adrenal adenoma-Pt 2 Wk 48 (n=0)	
Adrenal adenoma-Pt 3 Wk 12 (n=1)	-4.9
Adrenal adenoma-Pt 3 Wk 24 (n=0)	
Adrenal adenoma-Pt 3 Wk 48 (n=0)	
Adrenal adenoma-Pt 4 Wk 12 (n=1)	1.1
Adrenal adenoma-Pt 4 Wk 24 (n=0)	
Adrenal adenoma-Pt 4 Wk 48 (n=0)	
Adrenal adenoma-Pt 5 Wk 12 (n=1)	-0.4
Adrenal adenoma-Pt 5 Wk 24 (n=0)	

Adrenal adenoma-Pt 5 Wk 48 (n=0)	
Ectopic ACTH syndrome-Pt 1 Wk 12 (n=1)	2.9
Ectopic ACTH syndrome-Pt 1 Wk 24 (n=1)	12.9
Ectopic ACTH syndrome-Pt 1 Wk 48 (n=1)	11.1
Ectopic ACTH syndrome-Pt 2 Wk 12 (n=0)	
Ectopic ACTH syndrome-Pt 2 Wk 24 (n=0)	
Ectopic ACTH syndrome-Pt 2 Wk 48 (n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 12(n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 24 (n=0)	
Ectopic ACTH syndrome-Pt 3 Wk 48 (n=0)	

Absolute change from baseline in cardiovascular-related metabolic parameter, sitting blood pressure (BP) at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Sitting systolic BP	Sitting diastolic BP
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.	Patients in this arm took the study drug, osilodrostat.

Number of Participants Analyzed [units: participants]	7	7
Absolute change from baseline in cardiovascular-related metabolic parameter, sitting blood pressure (BP) at individual level (units: mmHg)		
AIMAH-Patient (Pt) 1Wk 12 (n =1, 1)	-44.3	-31.0
AIMAH-Patient (Pt) 1 Wk 24 (n =1, 1)	-48.34	-32.66
AIMAH-Patient (Pt) 1 Wk 48 (n =1, 1)	-40.34	-19.0
Adrenal adenoma-Pt 1 Wk 12 (n=1,1)	11.67	-3.67
Adrenal adenoma-Pt 1 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 1 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 2 Wk 12 (n=1,1)	-50.67	-37.0
Adrenal adenoma-Pt 2 Wk 24 (n=1,1)	-32.33	-26.66
Adrenal adenoma-Pt 2 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 3 Wk 12 (n=1,1)	-16.0	-6.67
Adrenal adenoma-Pt 3 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 3 Wk 48 (n=0,0)		

Adrenal adenoma-Pt 4 Wk 12 (n=1,1)	-6.67	7.33
Adrenal adenoma-Pt 4 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 4 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 5 Wk 12 (n=1,1)	11.0	3.33
Adrenal adenoma-Pt 5 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 5 Wk 48 (n=0,0)		
Ectopic ACTH syndrome-Pt 1 Wk 12(n=1,1)	-17.67	-13.67
Ectopic ACTH syndrome-Pt 1 Wk 24 (n=1,1)	4.33	4.0
Ectopic ACTH syndrome-Pt 1 Wk 48 (n=1,1)	-1.0	-0.67
Ectopic ACTH syndrome-Pt 2 Wk 12 (n=0,0)		
Ectopic ACTH syndrome-Pt 2 Wk 24 (n=0,0)		
Ectopic ACTH syndrome-Pt 2 Wk 48 (n=0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 12 (n=0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 24 (n=0,0)		
Ectopic ACTH syndrome-Pt 3 Wk 48 (n=0,0)		

Percentage change from baseline in cardiovascular-related metabolic parameter, sitting blood pressure (BP) at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Sitting systolic BP	Sitting diastolic BP
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7	7
Percentage change from baseline in cardiovascular-related metabolic parameter, sitting blood pressure (BP) at individual level (units: percentage change)		
AIMAH-Patient (Pt) 1Wk 12 (n =1, 1)	-31.1	-32.5
AIMAH-Patient (Pt) 1 Wk 24 (n =1, 1)	-33.9	-34.3
AIMAH-Patient (Pt) 1 Wk 48 (n =1, 1)	-28.3	-19.9
Adrenal adenoma-Pt 1 Wk 12 (n=1,1)	9.2	-4.1
Adrenal adenoma-Pt 1 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 1 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 2 Wk 12 (n=1,1)	-31.3	-33.2
Adrenal adenoma-Pt 2 Wk 24 (n=1,1)	-20.0	-23.9

Adrenal adenoma-Pt 2 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 3 Wk 12 (n=1,1)	-12.3	-8.9
Adrenal adenoma-Pt 3 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 3 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 4 Wk 12 (n=1,1)	-4.3	9.9
Adrenal adenoma-Pt 4 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 4 Wk 48 (n=0,0)		
Adrenal adenoma-Pt 5 Wk 12 (n=1,1)	9.3	5.1
Adrenal adenoma-Pt 5 Wk 24 (n=0,0)		
Adrenal adenoma-Pt 5 Wk 48 (n=0,0)		
Ectopic ACTH syndrome-Pt 1 Wk 12(n=1,1)	-14.1	-16.5
Ectopic ACTH syndrome-Pt 1 Wk 24 (n=1,1)	3.4	4.8
Ectopic ACTH syndrome-Pt 1 Wk 48 (n=1,1)	-0.8	-0.8
Ectopic ACTH syndrome-Pt 2 Wk 12 (n=0,0)		
Ectopic ACTH syndrome-Pt 2 Wk 24 (n=0,0)		
Ectopic ACTH syndrome-Pt 2 Wk 48 (n=0,0)		

Ectopic ACTH syndrome-Pt 3 Wk 12 (n=0,0)
Ectopic ACTH syndrome-Pt 3 Wk 24 (n=0,0)
Ectopic ACTH syndrome-Pt 3 Wk 48 (n=0,0)

Total scores in Patient-Reported Outcomes Health-related quality of life (QoL) as assessed by Cushing QoL at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	7
Total scores in Patient-Reported Outcomes Health-related quality of life (QoL) as assessed by Cushing QoL at individual level (units: scores on a scale)	
AIMAH-Patient 1: Week (Wk) 12 (n=1)	48
AIMAH-Patient 1: Wk 24 (n=1)	51
AIMAH-Patient 1: Wk 48 (n=1)	47
Adrenal adenoma-Patient 1: Wk 12(n=1)	29

Adrenal adenoma-Patient 1: Wk 24 (n = 0)	
Adrenal adenoma-Patient 1: Wk 48 (n = 0)	
Adrenal adenoma-Patient 2: Wk 12(n=1)	18
Adrenal adenoma-Patient 2: Wk 24 (n = 1)	22
Adrenal adenoma-Patient 2: Wk 48 (n =0)	
Adrenal adenoma-Patient 3: Wk 12 (n =1)	29
Adrenal adenoma-Patient 3: Wk 24 (n = 0)	
Adrenal adenoma-Patient 3: Wk 48 (n = 0)	
Adrenal adenoma-Patient 4: Wk 12 (n =1)	38
Adrenal adenoma-Patient 4: Wk 24 (n = 0)	
Adrenal adenoma-Patient 4: Wk 48 (n = 0)	
Adrenal adenoma-Patient 5: Wk 12 (n=1)	45
Adrenal adenoma-Patient 5: Wk 24 (n = 0)	
Adrenal adenoma-Patient 5: Wk 48 (n = 0)	
Ectopic corticotropin syndrome-Pt 1: Wk 12 (n =1)	31

Ectopic corticotropin syndrome-Pt 1: Wk 24 (n =1)	33
Ectopic corticotropin syndrome-Pt 1: Wk 48 (n =1)	23
Ectopic corticotropin syndrome-Pt 2: Wk 12 (n =0)	
Ectopic corticotropin syndrome-Pt 2: Wk 24 (n =0)	
Ectopic corticotropin syndrome-Pt 2: Wk 48 (n =0)	
Ectopic corticotropin syndrome-Pt 3: Wk 12 n =0)	
Ectopic corticotropin syndrome-Pt 3: Wk 24 (n =0)	
Ectopic corticotropin syndrome-Pt 3: Wk 48 (n =0)	

Total scores in Patient-Reported Outcomes Health-related quality of life (QoL) as assessed by Beck Depression Inventory II (BDI-II) depression score at individual level

(Time Frame: Baseline, Week 12 (day 85), Week 24 (day 169) and Week 48 (day 337))

	Osilodrostat
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.

Number of Participants Analyzed [units: participants]	7

Total scores in Patient-Reported Outcomes Health-related quality of life (QoL) as assessed by Beck Depression Inventory II (BDI-II) depression score at individual level
(units: scores on a scale)

AIMAH-Patient 1: Week (Wk) 12 (n =1)	4
AIMAH-Patient 1: Wk 24 (n =1)	15
AIMAH-Patient 1: Wk 48 (n =1)	12
Adrenal adenoma-Patient 1: Wk 12 (n =1)	33
Adrenal adenoma-Patient 1: Wk 24 (n = 0)	
Adrenal adenoma-Patient 1: Wk 48 (n = 0)	
Adrenal adenoma-Patient 2: Wk 12 (n =1)	35
Adrenal adenoma-Patient 2: Wk 24 (n =1)	37
Adrenal adenoma-Patient 2: Wk 48 (n = 0)	
Adrenal adenoma-Patient 3: Wk 12 (n =1)	30
Adrenal adenoma-Patient 3: Wk 24 (n = 0)	
Adrenal adenoma-Patient 3: Wk 48 (n = 0)	

Adrenal adenoma-Patient 4: Wk 12 (n =1)	26
Adrenal adenoma-Patient 4: Wk 24 (n = 0)	
Adrenal adenoma-Patient 4: Wk 48 (n = 0)	
Adrenal adenoma-Patient 5: Wk 12 (n =1)	10
Adrenal adenoma-Patient 5: Wk 24 (n = 0)	
Adrenal adenoma-Patient 5: Wk 48 (n = 0)	
Ectopic corticotropin syndrome-Pt 1: Wk 12 (n =1)	9
Ectopic corticotropin syndrome-Pt 1: Wk 24 (n =1)	10
Ectopic corticotropin syndrome-Pt 1: Wk 48 (n =1)	22
Ectopic corticotropin syndrome-Pt 2: Wk 12 (n =0)	
Ectopic corticotropin syndrome-Pt 2: Wk 24 (n =0)	
Ectopic corticotropin syndrome-Pt 2: Wk 48 (n =0)	
Ectopic corticotropin syndrome-Pt 3: Wk 12 (n =0)	

Ectopic corticotropin syndrome-Pt 3: Wk 24 (n =0)
Ectopic corticotropin syndrome-Pt 3: Wk 48 (n =0)

Plasma concentrations of Osilodrostat (LCI699) at Week 0

(Time Frame: Week 0)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	1	8	0	0
Plasma concentrations of Osilodrostat (LCI699) at Week 0 (units: ng/mL) Mean ± Standard Deviation				
Week 0: 0.75 hour post-dose	0.971 ± N/A[123]	0.405 ± 0.673		
Week 0: 2 hours post-dose	5.11 ± N/A[123]	5.29 ± 4.94		
Week 0: 4 hours post-dose	3.77 ± N/A[123]	8.12 ± 2.36		

[1] N/A : not enough participants to calculate the standard deviation
[2] N/A : not enough participants to calculate the standard deviation
[3] N/A : not enough participants to calculate the standard deviation

Plasma concentrations of Osilodrostat (LCI699) at Week 1

(Time Frame: Week 1, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg

Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	1	5	1	2
Plasma concentrations of Osilodrostat (LCI699) at Week 1 (units: ng/mL) Mean ± Standard Deviation				
Week 1: 2 hours post-dose	10.9 ± N/A[12]	10.5 ± 6.57	21.3 ± N/A[12]	22.3 ± 14.2

[1] N/A : not enough participants to calculate the standard deviation
[2] N/A : not enough participants to calculate the standard deviation

Plasma concentrations of Osilodrostat (LCI699) at Week 2

(Time Frame: Week 2)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	2	2	2	2
Plasma concentrations of Osilodrostat (LCI699) at Week 2 (units: ng/mL) Mean ± Standard Deviation				
Week 2: 0.75 hour post-dose	3.89 ± 2.76	3.69 ± 3.3	33.1 ± 19.2	34.9 ± 34.6

Week 2: 2 hours post-dose	8.93 ± 2.36	14.3 ± 7.64	21.3 ± 4.53	33.6 ± 8.84
Week 2: 4 hours post-dose	7.01 ± 2.69	11.1 ± N/A[1]	13.6 ± 3.89	29.2 ± 0.354

[1] N/A : not enough participants to calculate the standard deviation

Plasma concentrations of Osilodrostat (LCI699) at Week 3

(Time Frame: Week 3, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	4	1	1	2
Plasma concentrations of Osilodrostat (LCI699) at Week 3 (units: ng/mL) Mean ± Standard Deviation				
Week 3: 2 hours post-dose	7.09 ± 2.07	7.62 ± N/A[12]	23.2 ± N/A[12]	37.8 ± 0.849

[1] N/A : not enough participants to calculate the standard deviation
[2] N/A : not enough participants to calculate the standard deviation

Plasma concentrations of Osilodrostat (LCI699) at Week 4

(Time Frame: Week 4, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.

Number of Participants Analyzed [units: participants]	4	2	0	2
Plasma concentrations of Osilodrostat (LCI699) at Week 4 (units: ng/mL) Mean ± Standard Deviation				
Week 4: 2 hours post-dose	4.08 ± 2.61	9.91 ± 3.53		24.0 ± 21.00

Plasma concentrations of Osilodrostat (LCI699) at Week 6

(Time Frame: Week 6, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	4	2	0	1
Plasma concentrations of Osilodrostat (LCI699) at Week 6 (units: ng/mL) Mean ± Standard Deviation				
Week 6: 2 hours post-dose	6.74 ± 2.42	12.7 ± 9.08		31.7 ± N/A[1]

[1] N/A : not enough participants to calculate the standard deviation

Plasma concentrations of Osilodrostat (LCI699) at Week 8

(Time Frame: Week 8, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	5	1	0	0
Plasma concentrations of Osilodrostat (LCI699) at Week 8 (units: ng/mL) Mean ± Standard Deviation				
Week 8: 2 hours post-dose	3.35 ± 2.75	13.9 ± N/A[1]		

[1] N/A : not enough participants to calculate the standard deviation

Plasma concentrations of Osilodrostat (LCI699) at Week 10

(Time Frame: Week 10, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	4	2	0	0
Plasma concentrations of Osilodrostat (LCI699) at Week 10 (units: ng/mL)				

Mean ± Standard Deviation		
Week 10: 2 hours post-dose	4.73 ± 1.26	11.3 ± 4.57

Plasma concentrations of Osilodrostat (LCI699) at Week 12

(Time Frame: Week 12)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	2	1	0	0
Plasma concentrations of Osilodrostat (LCI699) at Week 12 (units: ng/mL) Mean ± Standard Deviation				
Week 12: 0.75 hour post-dose	0.382 ± 0.171	3.1 ± N/A[123]		
Week 12: 2 hours post-dose	4.62 ± 2.51	9.98 ± N/A[123]		
Week 12: 4 hours post-dose	3.58 ± 2.3	6.57 ± N/A[123]		

[1] N/A : not enough participants to calculate the standard deviation
[2] N/A : not enough participants to calculate the standard deviation
[3] N/A : not enough participants to calculate the standard deviation

Plasma concentrations of Osilodrostat (LCI699) at Week 16

(Time Frame: Week 16, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg

Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	2	0	0	0
Plasma concentrations of Osilodrostat (LCI699) at Week 16 (units: ng/mL) Mean ± Standard Deviation				
Week 16: 2 hours post-dose	5.71 ± 1.33			

Plasma concentrations of Osilodrostat (LCI699) at Week 20

(Time Frame: Week 20, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	1	0	0	0
Plasma concentrations of Osilodrostat (LCI699) at Week 20 (units: ng/mL) Mean ± Standard Deviation				

Week 20: 2 hours post-dose	0.794 ± N/A[1]

[1] N/A : not enough participants to calculate the standard deviation

Plasma concentrations of Osilodrostat (LCI699) at Week 24

(Time Frame: Week 24, 2 hours post-dose)

	Osilodrostat 1mg	Osilodrostat 2mg	Osilodrostat 3mg	Osilodrostat 5mg
Arm/Group Description	Patients in this arm took 1mg of study drug, osilodrostat.	Patients in this arm took 2mg of study drug, osilodrostat.	Patients in this arm took 3mg of study drug, osilodrostat.	Patients in this arm took 5mg of study drug, osilodrostat.
Number of Participants Analyzed [units: participants]	2	0	0	0
Plasma concentrations of Osilodrostat (LCI699) at Week 24 (units: ng/mL) Mean ± Standard Deviation				
Week 24: 2 hours post-dose	6.51 ± 2.14			

Summary of Safety

Safety Results

All-Cause Mortality

	Osilodrostat N = 9
Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Total participants affected	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events (AEs) were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 68.0 weeks.
Additional Description	AE description; Any sign or symptom that occurs during the study treatment plus the 30 days post treatment
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment

	Osilodrostat N = 9
Arm/Group Description	Patients in this arm took

	the study drug, osilodrostat.
Total participants affected	4 (44.44%)
Cardiac disorders	
Myocardial infarction	1 (11.11%)
Endocrine disorders	
Adrenal insufficiency	2 (22.22%)
Infections and infestations	
Pneumonia	1 (11.11%)
Psychiatric disorders	
Psychiatric symptom	1 (11.11%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events (AEs) were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 68.0 weeks.
Additional Description	AE description; Any sign or symptom that occurs during the study treatment plus the 30 days post treatment
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Osilodrostat N = 9

Arm/Group Description	Patients in this arm took the study drug, osilodrostat.
Total participants affected	9 (100.00%)
Blood and lymphatic system disorders	
Iron deficiency anaemia	1 (11.11%)
Ear and labyrinth disorders	
Vertigo	1 (11.11%)
Endocrine disorders	
Adrenal insufficiency	5 (55.56%)
Steroid withdrawal syndrome	1 (11.11%)
Gastrointestinal disorders	
Abdominal distension	1 (11.11%)
Abdominal pain upper	1 (11.11%)
Constipation	2 (22.22%)
Dental caries	1 (11.11%)
Enterocolitis	1 (11.11%)
Stomatitis	1 (11.11%)
General disorders and administration site conditions	
Malaise	3 (33.33%)
Oedema peripheral	1 (11.11%)

Pyrexia	1 (11.11%)
Hepatobiliary disorders	
Primary biliary cholangitis	1 (11.11%)
Infections and infestations	
Cellulitis	1 (11.11%)
Nasopharyngitis	3 (33.33%)
Osteomyelitis	1 (11.11%)
Injury, poisoning and procedural complications	
Rib fracture	1 (11.11%)
Investigations	
Alanine aminotransferase increased	2 (22.22%)
Amylase increased	1 (11.11%)
Aspartate aminotransferase increased	2 (22.22%)
Blood alkaline phosphatase increased	2 (22.22%)
Gamma-glutamyltransferase increased	3 (33.33%)
Weight decreased	1 (11.11%)
Weight increased	1 (11.11%)
Metabolism and nutrition disorders	

Decreased appetite	1 (11.11%)
Dyslipidaemia	1 (11.11%)
Hypokalaemia	2 (22.22%)
Hypomagnesaemia	1 (11.11%)
Increased appetite	1 (11.11%)
Musculoskeletal and connective tissue disorders	
Arthralgia	1 (11.11%)
Nervous system disorders	
Dizziness	1 (11.11%)
Psychiatric disorders	
Anxiety	1 (11.11%)
Insomnia	1 (11.11%)
Mood altered	1 (11.11%)
Nightmare	1 (11.11%)
Reactive psychosis	1 (11.11%)
Skin and subcutaneous tissue disorders	
Alopecia	1 (11.11%)
Dermal cyst	1 (11.11%)
Dermatitis acneiform	2 (22.22%)
Pruritus	2 (22.22%)
Rash	2 (22.22%)
Vascular disorders	
Peripheral coldness	1 (11.11%)

Other Relevant Findings

None

Conclusion:

- A rapid decrease in mUFC was observed in all 9 patients with CS except for CD regardless of the disease type, as well as with/without prior metyrapone treatment.
- Of the 7 patients who completed Week-12, 6 patients were complete responders and 1 patient was a partial responder.
- Osilodrostat demonstrated a clinically relevant effect with a short onset and efficacy maintained during the observed period in reducing the biochemical parameters of hypercortisolism (i.e. urinary, and serum cortisol).
- No clinically relevant changes were observed in ACTH, and other adrenal steroid hormones at post-baseline.
- Improvements in most cardiovascular-related metabolic parameters were observed at Week-12 in the majority of patients despite the short exposure of osilodrostat.
- Osilodrostat was generally well-tolerated with no new safety signal.
- AESIs anticipated based on the mechanism of action of osilodrostat, which were generally well managed with dose reduction/interruption and/or concomitant medication.

Date of Clinical Trial Report

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