



## Clinical trial results:

**An open-label, multi-center, roll-over study to assess long-term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis-sponsored osilodrostat (LCI699) study and are judged by the investigator to benefit from continued treatment with osilodrostat**

### Summary

EudraCT number	2017-002840-34
Trial protocol	AT DE FR ES BG BE NL PL IT
Global end of trial date	16 November 2023

### Results information

Result version number	v1 (current)
This version publication date	01 December 2024
First version publication date	01 December 2024

### Trial information

#### Trial identification

Sponsor protocol code	CLCI699C2X01B
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03606408
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Recordati AG
Sponsor organisation address	Uferstrasse 90, , Basel, Switzerland, 4057
Public contact	Clinical Trial Information Desk, Recordati AG, clinicaltrials.endocrinology@recordati.com
Scientific contact	Clinical Trial Information Desk, Recordati AG, clinicaltrials.endocrinology@recordati.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	29 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2023
Global end of trial reached?	Yes
Global end of trial date	16 November 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate long-term safety data based on frequency and severity of AEs/SAEs

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	China: 10
Country: Number of subjects enrolled	Costa Rica: 3
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	Türkiye: 6

Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	127
EEA total number of subjects	47

Notes:

<b>Subjects enrolled per age group</b>	
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)	119
From 65 to 84 years	8
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

There was no screening period for the study, eligible patients were able to start study treatment as soon as they were enrolled. The first study visit was scheduled at the same time as the last study visit of the prior Novartis-sponsored study.

### Period 1

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

Blinding implementation details:

Not Applicable

### Arms

Arm title	baseline
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Arm description: -

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

Dosage and administration details:

Patients took the same Osilodrotat dose taken in he last day of previous Novartis study

<b>Number of subjects in period 1</b>	baseline
Started	127
Completed	127

### Period 2

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

### Arms

<b>Arm title</b>	Osilodrostat
Arm description:	
Patients were administered with osilodrostat, in the form of film-coated tablets for oral administration in 3 different strengths: 1 mg, 5 mg, and 10 mg. The patients received the same dose as they had been receiving in the prior Novartis-sponsored study. Dose modifications were allowed, up to a maximum of 30 mg twice a day	
Arm type	Experimental
Investigational medicinal product name	Osilodrostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Patients were administered with osilodrostat, in the form of film-coated tablets for oral administration in 3 different strengths: 1 mg, 5 mg, and 10 mg. The patients received the same dose as they had been receiving in the prior Novartis-sponsored study. Dose modifications were allowed, up to a maximum of 30 mg twice a day.

<b>Number of subjects in period 2</b>	Osilodrostat
Started	127
Completed	99
Not completed	28
Adverse event, serious fatal	1
Consent withdrawn by subject	7
Physician decision	4
Adverse event, non-fatal	13
New therapy for study indication	1
Lack of efficacy	2

## Baseline characteristics

### Reporting groups

Reporting group title	baseline
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Reporting group description: -

Reporting group values	baseline	Total	
Number of subjects	127	127	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	119	119	
From 65-84 years	8	8	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	44.2		
standard deviation	± 12.39	-	
Gender categorical			
Units: Subjects			
Female	95	95	
Male	32	32	

## End points

### End points reporting groups

Reporting group title	baseline
Reporting group description: -	
Reporting group title	Osilodrostat
Reporting group description: Patients were administered with osilodrostat, in the form of film-coated tablets for oral administration in 3 different strengths: 1 mg, 5 mg, and 10 mg. The patients received the same dose as they had been receiving in the prior Novartis-sponsored study. Dose modifications were allowed, up to a maximum of 30 mg twice a day	

### Primary: Number of participants with adverse/serious adverse events

End point title	Number of participants with adverse/serious adverse events <sup>[1]</sup>
End point description: To evaluate long-term safety data with osilodrostat treatment (Frequency and severity of adverse events (AEs)/serious adverse events (SAEs))	
End point type	Primary
End point timeframe: up to 5 years.	

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: Descriptive statistics were used for all variables, as appropriate. Continuous variables were summarised by the number of observations, mean, standard deviation (SD), median, upper and lower quartiles (as applicable), minimum, and maximum. Categorical variables were summarised by the number of non-missing observations and percentages for each category. The baseline visit (W1D1) of this study corresponded to the end of treatment (EOT) visit in the respective prior Novartis-sponsored study.

End point values	baseline	Osilodrostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	127		
Units: participants				
number (not applicable)				
adverse event	0	115		
treatment related AEs	0	50		
adverse events of CTCAE grade >3	0	34		
Treatment-related AEs of CTCAE Grade ≥ 3	0	3		
Serious adverse events	0	35		
Treatment-related SAEs	0	4		
Fatal SAEs	0	2		
Treatment-related fatal SAEs	0	0		
Adverse events leading to discontinuation	0	14		
Adverse events leading to dose interruption or adj	0	56		
Treatment-related AEs leading to dose interruption	0	35		
Adverse events requiring additional therapy	0	94		

Treatment-related AEs requiring additional therapy	0	17		
Adverse events of special interest (AESIs)	0	51		
Treatment-related AESIs	0	29		
treatment related AEs leading to discontinuation	0	5		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Patients With Clinical Benefit

End point title	Percentage of Patients With Clinical Benefit
End point description:	
Proportion of patients with clinical benefit as assessed by the Investigator at scheduled visits based on medical check-up and lab values such as Urine Free Cortisol.	
End point type	Secondary
End point timeframe:	
up to 5 years	

End point values	baseline	Osilodrostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	127		
Units: participants				
number (not applicable)				
week 1	0	127		
week 12	0	122		
week 24	0	119		
week 36	0	114		
week 48	0	103		
week 96	0	744		
week 144	0	52		
end of treatment	0	99		

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

up to 5 years

Adverse event reporting additional description:

As the objective of the study was to evaluate the long-term safety of osilodrostat, the patients have been analysed all together, regardless the drug dosage.

Two (1.6%) patients experienced SAEs with the outcome of death during the study; these occurred during the 30-day post-treatment follow-up period (before the Safety Follow-up). These deaths w

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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### Reporting groups

Reporting group title	treatment
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Reporting group description: -

Serious adverse events	treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 127 (27.56%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACTH-producing pituitary tumour			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour benign			

subjects affected / exposed	3 / 127 (2.36%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal neoplasm			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver function test abnormal			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Paralysis			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal vein thrombosis			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary dilatation			

subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	3 / 127 (2.36%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 127 (1.57%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Flank pain			

subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Appendicitis			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>COVID-19</b>			
subjects affected / exposed	7 / 127 (5.51%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 2		
<b>Pneumonia</b>			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pneumonia bacterial</b>			
subjects affected / exposed	1 / 127 (0.79%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 127 (90.55%)		
<b>Investigations</b>			
Cortisol free urine increased			
subjects affected / exposed	13 / 127 (10.24%)		
occurrences (all)	0		
SARS-CoV-2 test positive			
subjects affected / exposed	13 / 127 (10.24%)		
occurrences (all)	0		
<b>Vascular disorders</b>			

Hypertension subjects affected / exposed occurrences (all)	11 / 127 (8.66%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)	10 / 127 (7.87%) 0  16 / 127 (12.60%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)  Blood corticotrophin increased subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)	9 / 127 (7.09%) 0  8 / 127 (6.30%) 0  9 / 127 (7.09%) 0  8 / 127 (6.30%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  nausea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	9 / 127 (7.09%) 0  13 / 127 (10.24%) 0  14 / 127 (11.02%) 0  9 / 127 (7.09%) 0		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 127 (5.51%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	7 / 127 (5.51%)		
occurrences (all)	0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	16 / 127 (12.60%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 127 (7.09%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	11 / 127 (8.66%)		
occurrences (all)	0		
Infections and infestations			
COVID-19			
subjects affected / exposed	29 / 127 (22.83%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	11 / 127 (8.66%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	12 / 127 (9.45%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	10 / 127 (7.87%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	7 / 127 (5.51%)		
occurrences (all)	0		
Metabolism and nutrition disorders			



Decreased appetite subjects affected / exposed occurrences (all)	9 / 127 (7.09%) 0		
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**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2021	Implementation of additional safety assessments as detailed in protocol amendment 1. Introduction of interim analysis for safety.
14 April 2023	Implementation of protocol amendment 2. Identification of the data from parent studies to complete baseline visits (W1D1). Deletion of outputs for Sections 10, 11, and 12.

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported