An Open-Label Extension Study of the Safety of Relacorilant (CORT125134) in the Treatment of the Signs and Symptoms of Endogenous Cushing Syndrome

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Primary Objectives: Safety Assessments: Effect of Administration of Relacorilant on: • Incidence of TEAEs (assessed monthly): TEAEs, SAEs, treatment-related TEAEs, TEAEs leading to early discontinuation of study treatment• Clinical laboratory tests...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Adrenal gland disorders
Study type	Interventional

Summary

ID

NL-OMON53993

Source
ToetsingOnline

Brief title
CORT125134-452 (ICON 0115/0011)

Condition

- Adrenal gland disorders
- Metabolism disorders NEC

Synonym
Cushing's syndrome, excess of cortisol, hypercortisolism

Research involving
Human

Sponsors and support

Primary sponsor: Corcept Therapeutics Incorporated
Source(s) of monetary or material Support: Corcept Therapeutics

Intervention

Keyword: Cushing's syndrome, extension study, open-label, Relacorilant

Outcome measures

Primary outcome

Endpoints/Study Outcomes related to Primary Objectives:

• Incidence of treatment-emergent adverse events (TEAEs) (assessed monthly):

TEAEs, serious TEAEs (SAEs), treatment-related TEAEs, TEAEs leading to early

discontinuation of study treatment.

• Changes from Baseline in clinical laboratory tests (hematology and chemistry

panels)

• Changes from Baseline in physical examinations and vital sign measurements

• Changes from Baseline in electrocardiograms (ECGs) (12-lead)(including QTcF

interval, QRS complex, PR interval, and heart rate)

• Changes from Baseline in pituitary tumors based on magnetic resonance imaging

(MRI) scans in patients with Cushing disease.

Endpoints/Study Outcomes related to Exploratory Objectives:

• Changes from Baseline in the following:

- Glycated hemoglobin (HbA1c) and insulin resistance indices in patients with

diabetes mellitus (DM) or glucose intolerance at Baseline in the parent study.

- Blood pressure (BP) by ambulatory BP measurements (ABPM) in patients with

uncontrolled hypertension (HTN) at Baseline in the parent study and in patients with controlled HTN taking >1 anti-HTN medication(s).

- Body weight and waist circumference.

- Quality-of-life (CushingQoL) questionnaire.

- Biochemical marker of bone remodeling: serum osteocalcin

- Hypothalamic-pituitary-adrenal (HPA) axis markers: plasma adrenocorticotropic hormone (ACTH) and serum cortisol.

- Cortisol concentration: 24 hour urinary free cortisol (UFC) test with creatinine (for patients who completed the CORT125134-455 GRACE study only) and late-night salivary-cortisol test.

- Lipid metabolism panel: total cholesterol, low-density lipoprotein cholesterol, high density lipoprotein cholesterol, very low density lipoprotein-cholesterol, and triglycerides).

- Sex steroid hormone and gonadotropins: estradiol, total and free testosterone, follicle-stimulating hormone, luteinizing hormone.

- Menstrual-cycle assessments (premenopausal women not taking hormonal contraceptive medication): age at menarche, current pattern of menses, duration of vaginal bleed.

- Dual-energy X-ray absorptiometry (DXA) scans.

- Coagulation markers.

- Clinical appearance (based on review of patient photographs): Cushingoid appearance and striae (Patient photographs will be collected for patients who completed the CORT125134-455 GRACE study only.).

• Measurement of messenger ribonucleic acid (mRNA) expression of GR activity

biomarkers (e.g., glucocorticoid-induced gene panel).

Secondary outcome

Not applicable

Study description

Background summary

Endogenous Cushing syndrome is a rare multisystem disorder that results from overproduction of the glucocorticoid hormone cortisol. In both adults and children, Cushing syndrome is most commonly caused by an ACTH-secreting pituitary tumor (Cushing disease). Other forms of Cushing syndrome result from autonomous production of cortisol from adrenal cortical tumors or overproduction of ACTH from non-pituitary tumors (ectopic ACTH syndrome). The only curative treatment is resection of the tumor source responsible for the excess cortisol.

Currently, three medical therapies are approved by the United States (US) Food and Drug Administration (FDA) for treatment of endogenous Cushing syndrome: (1) mifepristone (Korlym®), approved for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have type 2 diabetes mellitus (DM) or glucose intolerance and have failed surgery or are not candidates for surgery, (2) pasireotide (Signifor), a somatostatin receptor agonist approved for the treatment of adult patients with Cushing disease for whom pituitary surgery is not an option or has not been curative and (3) osilodrostat (Isturisa), a cortisol-synthesis inhibitor approved for the treatment of adult patients with Cushing*s disease for whom pituitary surgery is not an option or has not been curative. In Europe, drugs approved for the treatment of Cushing syndrome include aminoglutethimide (Orimeten), ketoconazole (Nizoral), metyrapone (Metopirone), osilodrostat (Isturisa), mitotane (Lysodren), and pasireotide (Signifor).

Relacorilant is a potent, selective GR antagonist. The mechanism of action of relacorilant is similar to that of mifepristone, with the exception that relacorilant does not bind to the progesterone receptor. The potential advantage of relacorilant compared with mifepristone is its selective and potent GR antagonism, without anti progesterone effects, including endometrial hypertrophy and the potential for irregular vaginal bleeding.

This protocol is designed to allow therapy with relacorilant (CORT125134), a

potent, selective glucocorticoid receptor (GR) antagonist, in patients with endogenous Cushing syndrome who meet the entry criteria for this extension study, who complete their last treatment visit in a Corcept-sponsored study of relacorilant (referred to as the *parent* study) , and who, in the Investigator*s opinion, will benefit from relacorilant treatment.

Study objective

Primary Objectives: Safety Assessments: Effect of Administration of Relacorilant on:

• Incidence of TEAEs (assessed monthly): TEAEs, SAEs, treatment-related TEAEs, TEAEs leading to early discontinuation of study treatment
• Clinical laboratory tests (hematology and chemistry panels)
• Physical examinations and vital sign measurements
• ECGs (12-lead) (including QTcF interval, QRS complex, PR interval, and heart rate) at Baseline and End-of-treatment.
• Pituitary tumors based on MRI scans in patients with Cushing disease.

Exploratory Objectives : Assessments of Treatment Effect
• Effect of administration of relacorilant on the following:

- HbA1c and insulin resistance indices in patients with DM or glucose intolerance at Baseline in the parent study.
- Blood pressure (BP) by ambulatory BP measurements (ABPM) in patients with uncontrolled hypertension (HTN) at Baseline in the parent study and in patients with controlled HTN taking >=1 anti-HTN medication(s).
- Body weight and waist circumference.
- Quality-of-life (CushingQoL) questionnaire.
- Biochemical markers of bone remodeling: serum osteocalcin.
- HPA axis markers: plasma ACTH and serum cortisol.
- Cortisol concentration: 24-hour UFC test with creatinine (for patients who completed the CORT125134-455 GRACE study only) and late-night salivary-cortisol test.
- Lipid-metabolism panel: total cholesterol, low-density lipoprotein cholesterol, high density lipoprotein cholesterol, very low density lipoprotein-
cholesterol, and triglycerides).
- Sex-steroid hormone and gonadotropin levels: estradiol, total and free testosterone, follicle-stimulating hormone, luteinizing hormone.
- Menstrual-cycle assessments (premenopausal women not taking hormonal contraceptive medication): age at menarche, current pattern of menses, duration of vaginal bleed.
- DXA scans.
-Coagulation markers.
- Clinical appearance (based on review of patient photographs): Cushingoid appearance and striae (Patient photographs will be collected for

patients who completed the CORT125134-455 GRACE study only.).

• Measurement of mRNA expression of GR-activity biomarkers (e.g. glucocorticoid-induced gene panel).

Study design

This is an open-label, single-arm, extension study designed to evaluate the long-term safety and therapeutic effect of orally administered relacorilant in patients with endogenous Cushing syndrome.

Intervention

Study drug is defined as relacorilant.

Patients will be dosed at the level of the last dosing visit in their parent Corcept-sponsored study as tolerated. If the last dose of relacorilant was >4 weeks from Day 1 of this study, or the patient enters from a blinded, placebo-controlled parent study, dosing will be titrated starting with 100 mg. The titration schedule will follow the titration schedule of the parent protocol. Suggested titration is as follows: Begin with 100 mg once daily. After 2 weeks, the dose of relacorilant will be increased to 200 mg and then increased every 4 weeks by 100 mg until the maximum tolerated dose from the parent study is achieved (not to exceed 400 mg), at the discretion of the investigator based on tolerability. Faster dose escalation for patients whose Cushing syndrome deteriorates during the study may be allowed on a case-by-case basis after discussion and approval by the medical monitor.
A patient*s relacorilant dose may be maintained, reduced, or increased at the discretion of the Investigator based on individual response and tolerability. Doses are increased and decreased in 100-mg increments.

Please refer to the protocol section 5 (page 40) Study Treatments and Management.

Study burden and risks

Glucocorticoid receptor antagonism is a proven mechanism of action for the treatment of the diabetes mellitus/impaired glucose tolerance (DM/IGT) secondary to hypercortisolism in adult patients with Cushing syndrome (Fleseriu et al. 2014). Because the mechanism of action of relacorilant is similar to that of mifepristone, with the exception that it does not bind the PR, relacorilant is expected to effectively treat Cushing syndrome, without the drawbacks of progesterone receptor antagonism that may result in untoward reproductive effects and/or interruption of therapy.

In the Phase 2 study (Study CORT125134-451) in patients with endogenous Cushing syndrome, relacorilant showed evidence of clinical benefit based on improvement of cortisol-excess*related comorbidities. The drug was generally well tolerated, with the upper bound on dosing being typically musculoskeletal complaints, a tolerability issue that patients can report.

Compared with the predecessor drug mifepristone, relacorilant offers two key safety advantages: lack of affinity for the PR, and lack of significant cortisol rise (a driver of hypokalemia in the marketed GR antagonist mifepristone).

Based on the mechanism of action of relacorilant, there is a theoretical risk of excessive GR antagonism, which could manifest by weakness, tiredness, dizziness, hypoglycemia, dehydration, weight loss, nausea, vomiting, diarrhea, and muscle aches. Since relacorilant does not affect the mineralocorticoid receptor, it is unlikely that hypotension would occur in the absence of concurrent treatment with antihypertensive medication. Because plasma glucocorticoid levels are not decreased with relacorilant administration, a biochemical diagnosis of excessive GR antagonism is not possible; diagnosis must rely on clinical assessment. In cases of suspected excess GR antagonism, study drug will be interrupted for 3 days and supplemental glucocorticoid will be given in high doses to overcome the GR antagonism.

The safety profile of relacorilant in study patients will be monitored by AE reporting, safety laboratory tests, physical examinations, vital signs, concomitant medication reviews, and pregnancy tests. ECGs will be performed at Screening, Baseline, and End-of-treatment (ECG at follow-up only if clinically indicated).

In vitro data indicate that relacorilant is metabolized by multiple CYP enzymes (CYP3A4, CYP2C8, and CYP3A5) and by carbonyl reductases. Data also indicate the potential for relacorilant to perpetuate drug drug interactions via inhibition of CYP3A and transporter pathways. Patients taking any prohibited medication are excluded from this study (refer to Section 5.3). If a concomitant medication is required to treat an AE, in selecting the appropriate concomitant medication, the Investigator must consider the risk of drug-drug interaction. The Medical Monitor should approve all concomitant medications required to treat an AE if there is a potential for drug-drug interaction. If necessary, the patient will be withdrawn from the study.

Study procedures include venous blood sampling and noninvasive procedures, including ECG recording, imaging, and vital-sign measurement. The total volume of blood collected will not exceed 50 mL per visit, unless the Investigator or designee considers additional unplanned collection(s) are required for safety laboratory tests.

More information on the risks and benefits of relacorilant is provided in the

Investigator*s Brochure

Contacts

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US
Scientific
Corcept Therapeutics Incorporated

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Have completed a Corcept-sponsored study of relacorilant in endogenous Cushing syndrome.
2. According to Investigator's opinion will benefit from treatment with relacorilant.
3. Provide written informed consent.
4. If a female of childbearing potential, patients must be willing to use a highly effective method of contraception from 30 days before study entry until 28 days after the last dose of study drug. Male patients with a female partner must agree to 2 forms of contraception, one of which must be a double-barrier

method, from study entry until 28 days after the last dose of study drug. Highly effective methods of contraception are detailed in the protocol.
5. Are willing to continue to refrain from using drugs that inhibit steroid biosynthesis by the adrenal cortex or ACTH secretion by a pituitary or extrapituitary ACTH secreting tumor.
6. Are able to return to the investigative site to complete the study evaluations outlined in the protocol.
7. For patients with Cushing syndrome due to an ACTH-secreting pituitary tumor, are able to obtain pituitary MRI imaging (up to 6 months before starting treatment in this study, or up to 6 weeks after start of treatment in this study) to assess changes in tumor size during dosing. A CT scan can be used instead in patients for whom MRI is contraindicated.
8. For patients entering the study >12 weeks after completing the last dose in the parent study, confirmation of hypercortisolism consistent with the criteria of the parent study is required.
9. For patients who received treatment for hypercortisolism after their last dose in the parent study, confirmation of hypercortisolism consistent with the criteria of the parent study is required.

Exclusion criteria

1. Have been prematurely discontinued from relacorilant study treatment in the parent study for any reason
2. Are planning to start another Cushing syndrome drug after starting participation in this extension study.
3. Have an acute or unstable medical problem that could be aggravated by relacorilant treatment or has known active COVID-19 infection at Screening .
4. Are taking the following medications from the times specified below before the Study CORT125134-452 Day 1 visit and/or through the entire study period:
• Medications used in the treatment of Cushing syndrome, with the exception of relacorilant, are prohibited:
- Adrenostatic medications: metyrapone, osilodrostat, ketoconazole, fluconazole, aminoglutethimide, or etomidate 4 weeks before Day 1 through the end of this study
- Neuromodulator drugs that act at the hypothalamic-pituitary level: serotonin antagonists (cyproheptadine, ketanserin, ritanserin), dopamine agonists (bromocriptine, cabergoline), gamma-aminobutyric acid agonists (sodium valproate), and somatostatin receptor ligands (octreotide long-acting release [LAR], pasireotide LAR, lanreotide) from 8 weeks before Day 1 through the end of this study. Use of short-acting somatostatin analogs (octreotide, pasireotide) from 4 weeks before Day 1 through the end of this study.
• Patients who require inhaled glucocorticoid use and have no alternative option if their condition
deteriorates during the study.
• Mifepristone, from 4 weeks before Day 1.

• Ongoing use of any strong CYP3A4 inducers during treatment with relacorilant.
• Has used mitotane prior to Day 1.
• Ongoing use of antidiabetic, antihypertensive, antidepressant, and/or lipid-lowering medications that are highly dependent on CYP3A for clearance and that cannot undergo dose modifications upon coadministration with strong CYP3A inhibitors.
5. Plans for prolonged regular use of systemic glucocorticoids from Day 1 through the end of the study.
6. Have received investigational treatment (drug, biological agent, or device) other than relacorilant within 4 weeks of study entry, or within 5 times the drug's half-life, whichever is longer.
7. Have a history of an allergic reaction or intolerance to relacorilant.
8. Have uncorrected clinically significant hypokalemia (potassium level of < 3 mEq/L) within 2 weeks before enrollment in this study (Day 1).
9. Have uncontrolled, clinically significant hypothyroidism or hyperthyroidism.
10. Have renal failure as defined by a serum creatinine of >=2.2 mg/dL.
11. Have elevated total bilirubin >1.5 × the ULN or elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >=3 × ULN.
12. Have a clinically significant ECG abnormality at baseline, which, in the opinion of the Investigator, will make the patient an unsuitable candidate for the study.
13. Have a confirmed baseline QT interval corrected using Fridericia's formula (QTcF) of >450 ms for males and >470 ms for females in the presence of a normal QRS interval (QRS <120 ms), a QTcF interval >500 ms with a wide QRS interval (>=120 ms),or a history of additional risk factors for torsades de pointes.
14. Has received stereotactic radiation therapy for a Cushing syndrome-related tumor within 24 months of Baseline or conventional pituitary radiation therapy within 36 months of Baseline.
15. Has undergone pituitary surgery <3 months prior to Screening.
16. Has plans for adrenalectomy or nodulectomy during the study, including follow-up.
17. Female who is pregnant or lactating.
18. Have an ongoing SAE that started in the parent study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-05-2022
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not yet known
Generic name:	Relacorilant

Ethics review

Approved WMO Date:	12-10-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	27-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-001616-30-NL
ClinicalTrials.gov	NCT03604198
CCMO	NL72513.078.21