# Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant

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Primary • To assess the efficacy of relacorilant for the treatment of endogenous Cushing syndrome based on BP control at Week 12 of the Randomized- Withdrawal (RW) phase compared with placebo• To assess the safety of relacorilant for the treatment...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Adrenal gland disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54706

**Source**
ToetsingOnline

**Brief title**
CORT125134-455 (ICON 0115/0015)

### Condition

- Adrenal gland disorders

**Synonym**
Cushing's syndrome

**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, Randomized-Withdrawl, Relacorilant

## Outcome measures

**Primary outcome**

The primary efficacy endpoint will be assessed in the RW phase. The study will be considered to have a positive outcome if the primary efficacy endpoint reaches statistical significance:

• In patients with hypertension, the proportion of patients with a loss of response with respect to hypertension from Visit OL22 to RW12 based on 24-hour ABPM as compared between relacorilant and placebo arms, where loss of response is defined as follows:

- In patients who met only the SBP response criterion, an increase in SBP >=5 mm Hg

- In patients who met only the DBP response criterion, an increase in DBP by >=5 mm Hg

- In patients who met both the SBP and DPB response criteria, an increase in either

SBP or DBP by >=5 mm Hg

- Any increase or modification in antihypertensive medication due to worsening

hypertension

• Patients discontinue treatment in RW phase for any reason.

• In all patients, assessment or safety based on treatment-emergent adverse events (TEAEs)

**Secondary outcome**

Please refer to protocol Am 5 05April 2023, section 3 Study Design: 3.6.2 Secondary Efficacy Endpoints. Other secondary efficacy endpoints are listed by study phase (RW or OL), and by the type of endpoint.

# 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 adrenocorticotropic hormone (ACTH) secretion pituitary tumor (Cushing disease). Other forms of Cushing syndrome result from autonomous production or cortisol from adrenal cortical tumors or overproduction or ACTH from non-pituitary tumors (ectopic ACTH syndrome). The only curative treatment is resection of the tumor cause of the excess cortisol. Depending on the nature of the underlying tumor (ie, benign versus malignant, localized versus metastatic), the selected treatment, radiotherapy, medical therapy, or a combination of these. Pharmacological treatment serves to control the disease after unsuccessful surgery or recurrence (Nieman et al. 2015). It may also be used to lower cortisol activity to improve a patient*s condition prior to surgery and is employed as interim therapy under specific circumstances, such as in patients waiting for radiotherapy to be effective (Cuevas-Ramos 2014). Currently, there are four United States (US) Food and Drug Administration (FDA) -approved medical therapies for endogenous Cushing syndrome. The first, mifepristone (Korlym®), was approved for the control of diabetes mellitus / impaired glucose tolerance (DM / IGT) secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have DM / IGT and have failed surgery or are not candidates for surgery. The second, pasireotide (Signifor®), is 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. The third, osilodrostat (Isturisa®) is 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. Relacorilant (CORT125134) is a potent, selective glucocorticoid receptor (GR) antagonist being developed for the treatment of Cushing syndrome. Relacorilant is a high-affinity antagonist of the GR (inhibition constant <1nM in a human GR binding assay and <10nM in a human functional assay). Although the mechanism of action of relacorilant is similar to that of mifepristone, relacorilant does not bind to the progesterone receptor (PR). Given its selective and potent GR antagonism, relacorilant has the potential advantage compared with mifepristone or not having any antiprogesterone effects, including endometrial hypertrophy and the potential for irregular vaginal bleeding.

## Study objective

Primary
• To assess the efficacy of relacorilant for the treatment of endogenous Cushing syndrome based on BP control at Week 12 of the Randomized- Withdrawal (RW) phase compared with placebo
• To assess the safety of relacorilant for the treatment of endogenous Cushing syndrome

Secondary
• To assess changes in cortisol excess-related comorbidities (including DM/IGT and body weight) in patients with endogenous Cushing syndrome treated with relacorilant over the RW phase

## Study design

This is a Phase 3, double-blind, placebo-controlled, RW study to assess the efficacy, safety, and PK of relacorilant in patients with endogenous Cushing syndrome and concurrent DM / IGT and / or uncontrolled hypertension.

## Intervention

Please refer to the protocol section 5 Study Treatments and Management

## Study burden and risks

Glucocorticoid receptor antagonism is a proven mechanism of action for the treatment of DM / IGT secondary to hypercortisolism in adult patients with Cushing syndrome (Fleseriu et al.2012). 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, but without the drawbacks or 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 antihypertensive medication. Because plasma glucocorticoid levels are not decreased with relacorilant administration, a biochemical diagnosis or 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 AEs, physical examinations, measurement of vital signs, 12-lead electrocardiograms (ECGs), and blood tests for clinical chemistry and hematology parameters.

Patients meeting response criteria will be randomized 1: 1 to continue relacorilant or receive a placebo equivalent (ie, have relacorilant withdrawn). Patients proceeding into the RW phase will be at risk for relapse of symptoms of Cushing syndrome, including worsening of diabetes, hypertension, and weight gain.

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 or CYP3A and transporter pathways. Patients taking any prohibited medication are excluded from this study (refer to section 5.4 of protocol). 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 must 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. During cannulation, more than 1 attempt may be needed to insert the cannula in a vein

or a patient and it is possible that bruising and / or inflammation may be experienced at the site of cannulation. The total volume of blood collected will not exceed 850 ml, 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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**Scientific**
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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

To enroll in the study, each patient must meet the following key inclusion criteria: 1. Male or female, 18 to 80 years of age, inclusive 2. Has a confirmed biochemical diagnosis of endogenous Cushing syndrome based on the

presence of at least 2 of the following: • UFC >= upper limit of normal (ULN) in at least 2 complete 24-hour tests within the screening window • Late-night salivary cortisol >= ULN in at least 2 tests (using a salivette) within the screening window (Note: Test is not appropriate for night shift workers and cannot be used to evaluate eligibility) • Lack of cortisol suppression (>=1.8 µg/dL serum cortisol) on either 1-mg overnight or 2-mg 48-hour dexamethasone suppression testing during Screening, or within 12 weeks before signing the informed consent 3. Has at least 2 of the following clinical signs and symptoms of Cushing syndrome: • Bodily characteristics of a Cushingoid appearance (e.g., facial rubor, moon facies, dorsocervical fat pad, supraclavicular fat pad) • Increased body weight or central obesity • Proximal muscle weakness • Low bone mass based on DXA scan • Psychiatric symptoms (including depression or psychosis) • Skin manifestations: violaceous striae, acne, and/or hirsutism • Easy bruisability 4. Has at least 1 of the following at Baseline: • DM (fasting plasma glucose >=126 mg/dL and/or 2-hour oGTT plasma glucose >=200 mg/dL at 2 hours or HbA1c >= 6.5%) or IGT (plasma glucose >=140 mg/dL and <=200 mg/dL on a 2-hour oGTT glucose) (American Diabetes Association 2020) • Uncontrolled hypertension (mean SBP >=135 to <=170 mm Hg and/or mean DBP >=85 to <=110 mm Hg)
based on 24-hour ABPM 5. If receiving medical treatment for DM/IGT or hypertension, there has been no increase in medication dosage for at least 4 weeks prior to Baseline assessment. 6. If receiving medical treatment for depression, there has been no increase in medication dosage for at least 6 weeks prior to Baseline 7. For women of childbearing potential, has a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline

## Exclusion criteria

Patients who meet any of the following criteria will not be permitted entry to the study: 1. Has severe, uncontrolled hypertension (mean SBP >=170 mm Hg or mean DBP >=110 mm Hg at Screening), based on 24-hour ABPM 2. Has poorly controlled DM (HbA1c >=12% at Screening) 3. Has a known *long term* history of both hypertension and diabetes (defined as both hypertension and diabetes diagnosed >=10 years prior to the initial diagnosis of endogenous CS) 4. Has a history of cyclic Cushing*s syndrome with fluctuating clinical manifestations. 5. Has DM Type 1. 6. Has abnormal liver test results (total bilirubin >= 1.5×ULN or elevated alanine aminotransferase or aspartate aminotransferase >=3×ULN at Baseline) 7. Has severe renal insufficiency (glomerular filtration rate <=29 mL/min at Baseline) 8. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism 9. Has prolonged QT interval corrected for heart rate using Fridericia*s equation (QTcF) (>=450 ms for men and >=470 ms for women) with normal QRS interval (<=120 ms) or QTcF interval >=500 ms with wide QRS interval (>=120 ms) 10. 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. 11. Has undergone pituitary

surgery <=3 months prior to Screening 12. Has used or plans to use any of the following treatments for Cushing syndrome within 4 weeks prior to Baseline: - Mifepristone - Adrenostatic medications: metyrapone, osilodrostat, ketoconazole, fluconazole, aminoglutethimide, or etomidate - Serotonin antagonists: cyproheptadine, ketanserin, or ritanserin - Dopamine agonists: bromocriptine or cabergoline - Gamma-aminobutyric acid agonists: sodium valproate - Short-acting somatostatin analogs: octreotide, lanreotide, or pasireotide 13. Has used or plans to use somatostatin receptor ligands: long-acting octreotide or pasireotide within 8 weeks prior to Baseline 14. Patients who require inhaled glucocorticoid use and have no alternative option if their condition deteriorates during the study. 15. Has adrenocortical carcinoma 16. Has used mitotane prior to Baseline. 17. Has ectopic Cushing syndrome and a life expectancy of <=3 years or receiving chemotherapy. 18. Has pseudo-Cushing syndrome. Patients with known or suspected pseudo-Cushing syndrome based on medical history (such as patients with severe obesity, major depression, or a history of alcoholism) should undergo a dexamethasone-CRH DDAVP stimulation test (Yanovski et al.1993, Giraldi et al. 2007, Yanovski et al. 1998) to rule-in or rule-out this possibility 19. Has taken any investigational drug within 4 weeks prior to Baseline, or within less than 5 times the drug*s half-life, whichever is longer 20. Ongoing use of antidiabetic, antihypertensive, antidepressant or lipid-lowering medications that are highly dependent on CYP3A for clearance and that cannot undergo dose modification upon coadministration with strong CYP3A inhibitors 21. Ongoing use of any strong CYP3A4 inducer or any other prohibited medications (Section 5.4.4) 22. Is pregnant or lactating 23. Is a female patient of childbearing potential (including all women <=50 years old, women whose surgical sterilization was performed <=6 months ago, and women who have had a menstrual period in the last 2 years) who cannot use a highly effective method of contraception (Section 4.6.2) 24. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug 25. Has a history of hypersensitivity or severe reaction to the study drug, to a similar class of drug, or to the study drug*s excipient 26. In the Investigator*s opinion, should not participate in the study or may not be capable of following the study schedule 27. Has known HIV or hepatitis B or C infection 28. Is a family member of one of the Sponsor*s employees, the Investigator, or the site staff directly working on the study 29. Has a history of unexplained vaginal bleeding or unexplained endometrial abnormalities.

# Study design

## Design

Study phase: 3

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| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 29-06-2020 |
| Enrollment: | 4 |
| Type: | Actual |

### Medical products/devices used

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

## Ethics review

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|---|---|
| Approved WMO Date: | 11-12-2018 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 19-06-2019 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 29-04-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

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| Approved WMO Date: | 25-05-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 01-05-2021 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 31-05-2021 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 31-03-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 15-04-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 23-05-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 28-12-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 01-02-2023 |
| Application type: | Amendment |

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| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 11-06-2023 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 10-08-2023 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 22-01-2024 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 08-05-2024 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 22-07-2024 |
| 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 | EUCTR2018-003096-35-NL |
| ClinicalTrials.gov | NCT03697109 |
| CCMO | NL68116.078.18 |

# Study results

Date completed: 15-04-2024

Results posted: 14-01-2025

**First publication**
13-12-2024